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No. 1

THE BLOOD IN SHOCK*

C. C. GUTHRIE, M.D.

INTRODUCTION

It has been stated that in shock liquid passes from the blood to the tissues,¹ resulting in alterations of physical condition, as increased specific gravity, red cell count, viscosity, and decrease in total blood volume.

In an investigation of experimental shock in dogs² the blood was studied to determine if such alterations occurred in the type of shock induced, and if there was a causal relation between blood change and shock.

METHODS AND RESULTS

Dogs under ether anesthesia were reduced to a state of shock, essentially by nerve stimulation.³ Some blood was lost by operative procedures and by taking samples for analyses, but in no case was such loss in itself of sufficient magnitude to induce shock. In typical cases the blood pressure was greatly lowered, the cardiac output was decreased—as indicated by diminished pulse pressure and volume—respiration was irregular, eye reflexes were present and slight if any tendency to recover was manifested on discontinuing the administration of ether. Alterations in reflex vasomotor phenomena were marked. Great differences in susceptibility to shock were exhibited by different dogs. Arterial blood samples were taken before and after shock. Coagulation was prevented by defibrination, and to control the findings a few samples were prevented from coagulating by the addition of potassium oxalate.

Specific gravity was determined by weighing. It moderately and progressively decreased. Taking into account the relatively high specific gravity of red blood corpuscles, it would seem that the reduction in the specific gravity of the blood was largely due to the dilution of the corpuscles from increase of plasma volume.

Hematokrit tests and *red cell counts* were performed in the usual manner. The volume per cent of red corpuscles and the number per unit of blood progressively decreased, indicating an increase in plasma volume.

Hemoglobin was estimated by several well-known methods, as those of Tallqvist and Sahli, but the method that gave the most accurate results was carried out by means of a Duboscq colorimeter. One c.c. of the first sample of

* Submitted for publication Feb. 22, 1918.

* From the Laboratories of Physiology, Pharmacology and Physiological Chemistry, University of Pittsburgh School of Medicine.

1. Malcolm, J. D. *Lancet*, London, 1905, **2**, 577. British Medical Research Committee, *ibid*, 1917, **1**, 502. Bainbridge, F. A. *Ibid*, 1917, **2**, 51.

2. Guthrie, C. C., and Guthrie, F. V. *Proc. Soc. for Exper. Biol. and Med.*, 1914, **11**, 148. Guthrie, C. C. *Proc. Am. Phys. Soc.* for 1917.

3. Guthrie, C. C. *Jour. Am. Med. Assn.*, 1917, **69**, 1394.

blood taken was added to and thoroughly shaken with 99 c c of water. Ten c c of this mixture were placed in each of the colorimeter cups and a reading taken to determine if the values on the two sides were the same. One cup was then emptied and refilled with a blood-water mixture prepared from a blood sample taken after shock was induced. It was read against the blood mixture from the sample taken before shock, contained in the other cup. The first sample, or standard, was taken as 100 per cent and the hemoglobin content of subsequent samples as expressed in terms of per cent of the standard. The hemoglobin values thus expressed, therefore, are comparative.

Concentration of hemoglobin in the blood progressively decreased, but in no instance was the change of sufficient magnitude to be considered as causally related to shock. The decline in concentration must have been due to entrance of liquid into the blood, as there was no evidence of loss of hemoglobin save that due to blood lost from operation and removed for examination.

Change in the colorimeter value of hemoglobin would influence the results. There is no evidence that material change of this character occurs in shock. To determine the possible influence of acidosis, experiments were made by adding lactic acid to blood and observing the effect on colorimeter readings. Until the reaction of the blood was altered in far greater degree than was observed in shock, in fact, not until the neutrality point had been passed, was there any material change in the colorimeter readings. When change was so induced, it was in the direction of increased value, and was associated with a change in the physical state of the solution as indicated by opalescence which passed to cloudiness.

Samples of blood differing only in oxygenation were diluted with water and tested colorimetrically without appreciable differences in values.

The working errors of all the tests were determined by making readings on a standard blood and a blood prepared by mixing equal parts of the standard blood and clear serum. The error in specific gravity was very slight. By repeated trials it was determined that the error in estimating hemoglobin by the Duboscq colorimeter method was under 2 per cent. The errors by the other methods, in our hands, were greater, in order of accuracy being hematocrit, Sahli's hemoglobin method, red cell count and Tallqvist's hemoglobin method. Of course, familiarity with methods and the personal equation are very large determining factors in the results of such comparative tests, and all we wish to indicate is that we were able in control tests to follow blood changes as determined by specific gravity, relative hemoglobin content, and blood sediment volume with comparatively small errors.

Viscosity was determined by measuring the rate of flow by forcing the liquid through a small bore tube with a constant pressure, and by means of a form of stalagmometer, gravity being the propelling force. Viscosity varies indirectly as the rate of flow, and alterations are expressed in comparative terms. In all instances observed, alterations in viscosity have been of moderate degree and have varied directly with specific gravity, blood sediment and hemoglobin. The magnitude of change in viscosity observed is too small to be of important significance, since enormous alterations in viscosity without profound circulatory impairment have been observed.⁴ In shock there has been no evidence of increase in tissue liquids, in fact, rather the tissues have more the appearance of being dry and shrunken. Also, there has been evidence of decrease in urine formation (no escape of urine during the experiment, and the bladder found to be empty at its conclusion), which would tend to result in retention of liquid by the blood.

Freezing Point—A form of Beckmann's apparatus was used for determining the freezing point of blood. Variations during the course of an experiment occurred, but the end results indicate a somewhat greater depression of the

4 Stewart, G. N. *Manual of Physiology*, New York, 1914, p. 23.

freezing point after shock Differences observed are considered too small to be of significant importance

Blood volume estimations were made from specific gravity, hematokrit, red cell count and hemoglobin findings The figures given are relative, and indicate dilution rather than actual blood volume, as they are not corrected for blood removed or lost An increase in volume indicates an increase of plasma resulting in a decreased concentration of red corpuscles

TABLE 1—RESULTS BEFORE AND IN SHOCK

	Before Shock Exp IV, May 2, 1912	In Shock	Before Shock Exp V, May 10, 1912	In Shock
Time	3 40	5 05	11 15	12 55
Blood pressure	148	27	178	60
Blood specific gravity	1 061	1 057	1 061	1 057
Blood freezing point	-0 634	0 646	-0 619	-0 643
Blood vol corpuscles*	51 6	45 0	51 6	45 0
Blood volume*	100 0	114 6	100 0	114 6
	Exp VII, May 23, 1912		Exp IX, Oct 31, 1912	
Time	2 05	3 30	3 10	5 15
Blood pressure	210	11	166	50
Blood specific gravity	1 058	1 054	1 067	1 067
Blood freezing point	-0 587	-0 585	-0 592	-0 617
Blood vol corpuscles*	46 6	40 0	100 0	100 0
Blood volume*	100 0	116 5	100 0	100 0
	Exp X, Nov 4, 1912		Exp XVII, May 19, 1917	
Time	2 35	4 55	2 47	4 58
Blood pressure	172	56	194	58
Blood specific gravity	1 065	1 053	1 068	1 062
Blood freezing point	-0 590	-0 620		
Blood sediment volume			64	56
Blood hemoglobin			100 0	80 9
Blood red cell count			10,389,600	7,992,000
Blood viscosity			100 0	96 3
Blood vol corpuscles*	58 3	38 3	63 4	53 3
Blood volume*	100 0	152 2	100 0	118 9, 114 2, 123 6
	Exp XVIII, May 26, 1917		Exp XX, June 2, 1917	
Time	3 00	4 58	2 38	4 55
Blood pressure	216	88	168	33
Blood specific gravity	1 064	1 060		
Blood sediment volume	58 5	52 0		
Blood hemoglobin	100 0	94 0	100 0	92 0
Blood viscosity	100 0	96 0		
Blood vol corpuscles*	56 6	50 0		
Blood volume*	100 0	113 2, 112 5, 106 3	100 0	107 1
* Calculated				
Blood pressure, mean arterial			Av 182	48
Specific gravity, determined by weighing			Av 1 063	1 059
Freezing point, degrees Centigrade			Av -0 604	-0 622
Blood sediment volume, per cent by hematokrit			Av 61 3	54 0
Hemoglobin, relative per cent by Duboscq colorimeter			Av 100 0	89 0
Red cell count, number per cubic millimeter			Av	
Viscosity, relative per cent			Av 100 0	96 2
Calculated volume corpuscles, from specific gravity			Av 54 7	45 3
Blood volume, calculated from specific gravity, sediment volume by hematokrit and hemoglobin			Av 100 0	117 6

TABLE 2—SUCCESSIVE BLOOD FINDINGS DURING THE COURSE OF AN EXPERIMENT

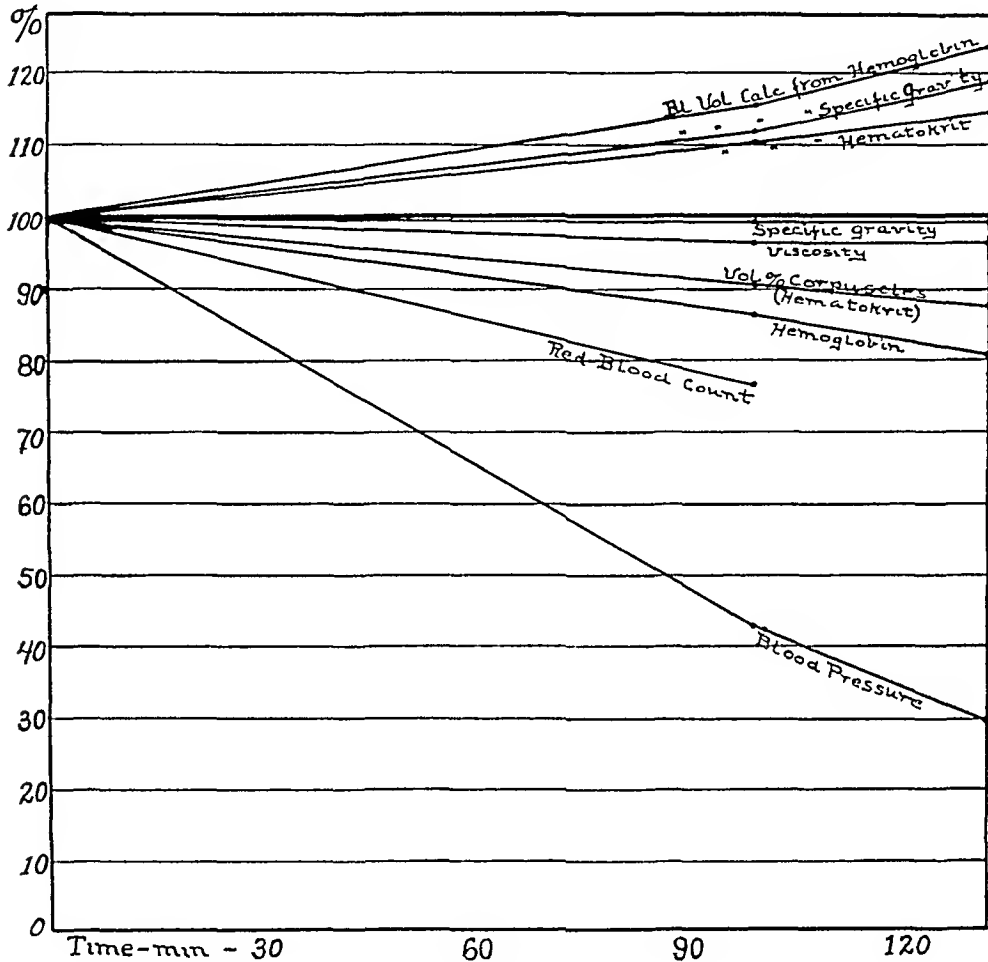
Time	11 15	11 45*	12 25	12 55
Blood pressure	178	200	109	60
Blood specific gravity	1 061	1 059	1 058	1 057
Blood freezing point	-0 619°	-0 628°	-0 629°	-0 643°

* 11 26 began strong nerve stimulation

DISCUSSION

The results show decrease in concentration of the red blood corpuscles. This is interpreted as due to entrance of liquid into the blood.

The degree and time of development of the shock induced varied more than the blood findings. Changes in the blood appear to bear a closer relation to length of experiment and amount of blood withdrawn than to the degree of shock. From this, and from the comparatively



Results of Experiment XVII, May 19, 1917, graphically expressed

small alterations in the blood, it seems clear that such changes in the blood at most were of minor causative significance in these experiments.

It is known, for example, that following hemorrhage, liquid enters the blood, the concentration of the formed elements (red cells), specific gravity and per cent of hemoglobin being thereby diminished. In shock associated with hemorrhage, therefore, this tendency would have to be more than counterbalanced for a concentration of the blood to occur. Injury of the capillary endothelium is known to result,

under certain conditions in the abnormal passage of liquid from the blood into the tissues. Such injury may result from toxic substances introduced into the blood stream, as peptone, or from asphyxiation, as venous obstruction, or temporary arterial obstruction. In shock there is no reason for surmising the presence of a toxic substance capable of such injury to the capillary endothelium, so it would be necessary to surmise an adequate degree of asphyxia.

No doubt the respiratory value of the circulation per unit of tissue is decreased under such conditions, but there is reason for believing that the respiratory demand of many of the tissues also is decreased, the reason being that tissue demand varies directly as activity, and in shock many tissue activities are diminished, as of voluntary muscles and kidneys. The question becomes a quantitative one and sufficiently accurate data for decisively answering it is lacking. As having an interesting relation to the question are observations on the relative susceptibility of different tissues to anemia and certain observations on the relation of preservation of activity of peripheral nervous mechanisms and of vascular endothelium under abnormal conditions. As to the relative susceptibility of vascular endothelium in decline of the respiratory value of the circulation, we have no direct experimental findings. It is generally held, however, that nervous mechanisms (cells and synapses) are the structures first to show impairment and loss of function under such conditions, and in profound shock, activity of even the more highly specialized nervous mechanisms, that is, the least resistant to anemia, as those of consciousness, may not be entirely lost. It would seem improbable, therefore, that at such a stage, much impairment of the capillary endothelium has occurred. It may be that certain capillary areas are more anemic than those of the brain, but in the event of such local impairment the decrease of blood in the areas affected would be against the probability of the escape of much blood liquid. In conformity with this, the superficial tissues appear bloodless and shrunken.

Some years ago experimental observations were made⁵ which seem to have a bearing on the question. The posterior trunk and extremities of dogs were removed, posterior to the kidneys, and perfused through the aorta with blood diluted with Locke's solution. The volume of the perfusion mixture was followed and muscular response to nerve stimulation was tested from time to time. There was little change in the blood mixture volume until marked decrease in muscular response occurred, at which time, or soon thereafter, the volume of the blood mixture rapidly decreased and the tissues became markedly edematous. In profound shock peripheral muscular activity and capability to

5 With Prof. Hugh McGuigan

respond to nerve stimulation is not lost, so from this standpoint, too, it would seem improbable that at such a time the capillary endothelium is seriously damaged

According to Bayliss,⁶ "Filtration is one of the factors in the production of lymph, since the intravascular pressure is greater than that in the tissue spaces, but Starling has insisted on the importance of osmotic pressure in addition. It is, in fact, clear that a rise in the osmotic pressure of the lymph, however this rise is produced, will result in the passage of water from the blood to the lymph and an increase in the volume present." He says that the entrance of liquid into the blood after hemorrhage is due to the higher osmotic pressure of blood than lymph, and that the decrease in blood pressure after hemorrhage permits the entrance of water into the blood from the tissues, normally the combined forces of mechanical and osmotic pressures of the blood balancing or overtopping that of the lymph.

However this may be, and differences of opinion as to the mechanism of lymph formation as well as to the relative osmotic pressures of blood and tissue liquid and lymph exist, the interpretation seems rather more in harmony with the view that in shock, conditions are more favorable for the entrance of liquid into, than passage from, the blood vessels.

The observations on the osmotic pressure of blood before and after shock, as indicated by depression of the freezing point, did not reveal alterations of magnitude considered adequate to warrant a conclusion as to the possible effect on blood volume. No similar observations were made on lymph, and therefore, no comparison of osmotic conditions in blood and lymph are possible in these experiments. But, since tissue activities were less after shock, and since such increased concentration in tissues is due to substances readily permeating the blood stream, and since there was a marked decrease in renal activity, it seems reasonable to conclude from the comparatively slight alterations in the osmotic pressure of the blood, that osmotic pressure of the tissue liquids was not greatly altered. The concentration of the blood following restoration of the circulation in the posterior trunk after temporary anemia (stasis or asphyxiation) induced by vascular occlusion concords with these views. And further support is afforded by the observation that after a period of restored circulation, concentration of the blood ceased and soon again began to diminish. (See Exper XXI, June 12, 1917.)

The rôle of acidosis in the interchange of liquid between the blood and tissue liquids⁷ should be considered, but in the absence of accurate

6 Bayliss, W. M. *Principles of General Physiology*, London, 1915, p. 165.

7 Fischer, Martin. *Edema and Nephritis*, New York, 1915.

data, no conclusions are possible. It would seem, however, to be extremely doubtful that the comparatively slight change in blood reaction observed in certain shocked animals would indicate a degree of tissue acidosis of magnitude sufficient to be of material influence.

In conclusion, we wish to emphasize that these observations were made chiefly in a search for conditions having possible causal relations to the type of shock investigated — not phenomena possibly resulting in late conditions resulting from shock, or conditions possibly occurring in other types of shock. It is not difficult to imagine types of shock in which decrease in total blood volume is a factor of consequential magnitude, as shock associated with hemorrhage, or with extensive tissue traumatization and destruction.

That concentration of the blood may be induced in shock is indicated by the following observation.

Experiment XXI, June 12, 1917. After the arterial blood pressure had been reduced to under 60 mm Hg, the thoracic aorta was temporarily occluded. Before aortic occlusion the relative per cent of hemoglobin had decreased. Following release of the aorta, that is, after the circulation was restored in an area temporarily rendered anemic, for a time the relative per cent of hemoglobin increased.

It is not certain from this one observation that an actual concentration occurred. But it seems probable, for considered serially, before aortic occlusion the percentages were 100, 87.7 and 75.7, and after, 94.3, 101 and 90.0. Since it is well known that circulation through a part previously subjected to profound anemia is associated with edema, this result is to be attributed to the anemia factor induced through aortic occlusion and not due to the condition of shock itself.

In such conditions, associated with marked decrease in blood volume, restoration of blood volume is indicated.⁸ But in shock not associated with such conditions the indications for such therapeutic measures are less clearly defined.

CONCLUSIONS

1. In the condition investigated, alterations in blood volume causatively were unimportant.

2. Evidence of entrance of liquid into the blood was obtained.

⁸ Guthrie, C. C. *Blood Vessel Surgery and Its Applications*, London, 1912, p. 347.

THE LIGATION OF CORONARY ARTERIES WITH ELECTROCARDIOGRAPHIC STUDY*

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CHICAGO

This article is based on a study of sixty-six dogs in which known myocardial lesions had been produced by the ligation of definite branches of the coronary arteries of the heart. While the experiments were made with the primary object of determining the change in the electrocardiograms brought about by these ligations, other results, anatomic and pathologic, are deemed worthy of brief mention.

Method—Dogs were anesthetized with ether and electrocardiograms taken. The chest was surgically prepared and a tracheal cannula introduced for positive pressure. An incision was made parallel to the sternum at about the left costosternal margin, from the third to the sixth rib, then to the left in the fifth interspace. The flap, including the deep muscle layer down to the ribs, was dissected back. Blunt scissors were pushed through the intercostal muscle in the fifth interspace into the pleural cavity, and this incision was carried from the sternum well lateralward. The third to the fifth rib, inclusive, were severed at the costosternal margin and the ribs retracted, thus affording a good exposure of the heart. This exposure was especially satisfactory for the ramus descendens anterior sinister. To ligate the circumflexus sinister to the best advantage the incision had to be carried especially far to the left side with the animal lying on the right side. To expose the right coronary artery an incision similar to the one described was made on the right side of the chest. The pericardium was slit as nearly as possible over the desired artery, which was ligated with strong linen. The pericardial sac and chest cavity were then closed as quickly as possible without regard to the pleura.

Electrocardiograms were taken before the ligations. Early in the work records were made immediately following the ligation and at intervals of ten minutes, over a period of thirty to forty minutes, except in two cases, in which observations were made over a period of four hours. There seemed to be no special advantage in taking these frequent records, so that later they were ordinarily taken at the end of the operation, which was usually from twenty to thirty minutes following the ligation, and then not for several hours.

During the postoperative periods, records were taken at varying intervals. In the first thirty animals the interval was from seven to ten days. Later, electrocardiograms were taken every day for the first week or ten days. After this period every week. Frequent observations in the early postoperative course were found to be desirable.

The dogs were watched for evidence of cardiac failure and were frequently tested for such condition by forced exercise. Signs of other diseases, such as infections, were also noted. In case of death, an early necropsy was performed, especial attention being paid to the lesions found in the heart, their location, extent and histologic structure.

* Submitted for publication Feb 16, 1918

* This investigation was aided by funds given by Madam C H McCormick and R T Crane, Jr

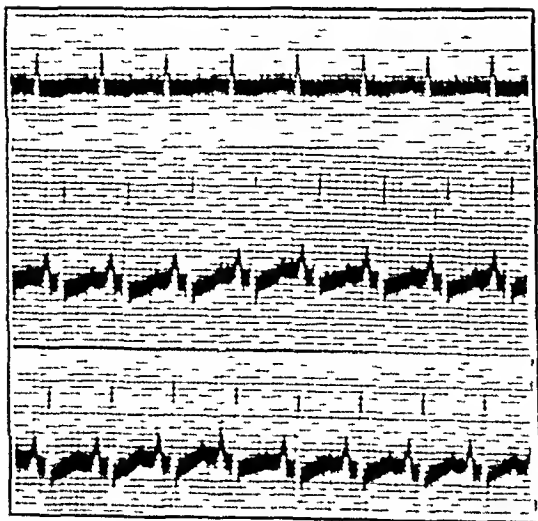


Fig 1

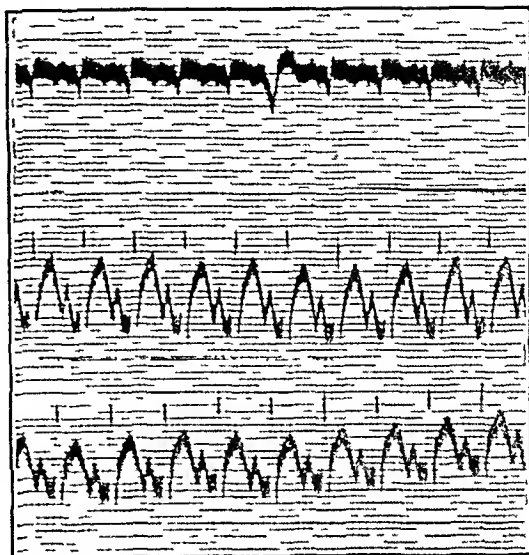


Fig 2

Fig 1—Normal electrocardiogram of a dog

Fig 2—Dog 48 The record was taken twenty-five minutes following the ligation of the ramus descendens anterior sinister and the first descending branch of the ramus circumflex sinister. The T-wave is markedly elevated—left ventricular extrasystole in Lead I.

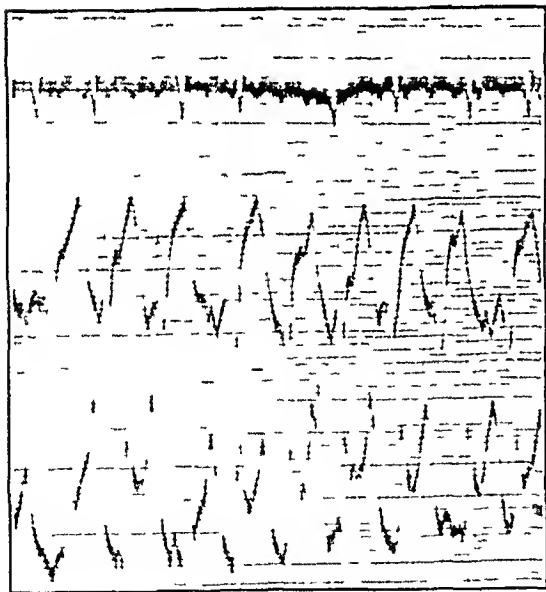


Fig 3

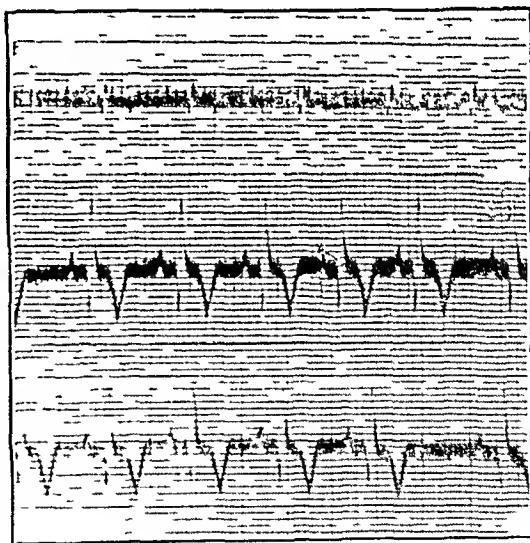


Fig 4

Fig 3—Dog 17 Record taken five minutes following the ligation of the ramus circumflexus sinister—auricular flutter, auricular rate 500, ventricular rate 166-250. The T-wave is elevated as in Figure 2.

Fig 4—Dog 40 The electrocardiogram was taken five days after the ligation of the ramus descendens anterior and the first descending branch of the ramus circumflexus sinister. The T-wave is sharply negative in Leads II and III. It was strongly positive immediately following operation.

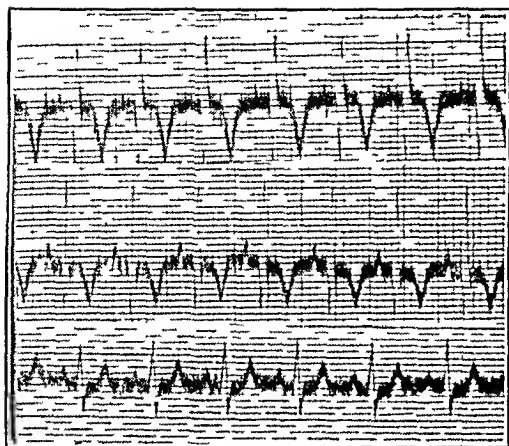


Fig 5

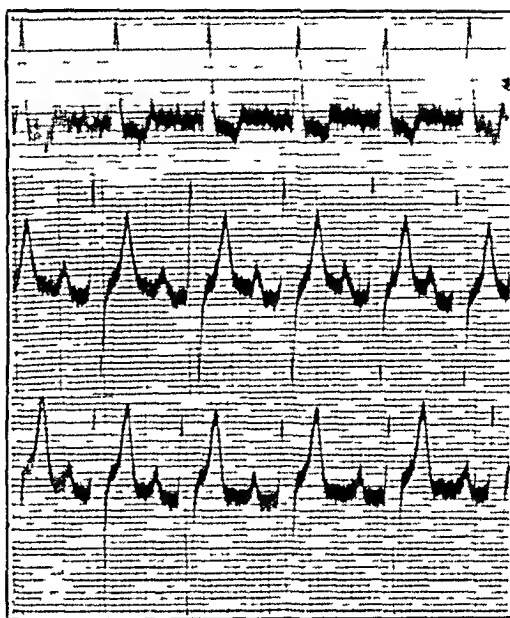


Fig 6

Fig 5—Dog 54 The electrocardiogram was taken two days after the ligation of the first two lateral branches of the ramus descendens anterior and the first descending branch of the ramus circumflexus sinister. The T-wave in Leads II and III is sharply negative. The T in Lead III has become positive.

Fig 6—Dog 29 The record was taken two days after the ligation of the right coronary artery. There is a left ventricular preponderance. The T-wave in Leads II and III has changed from a negative to a markedly positive phase.

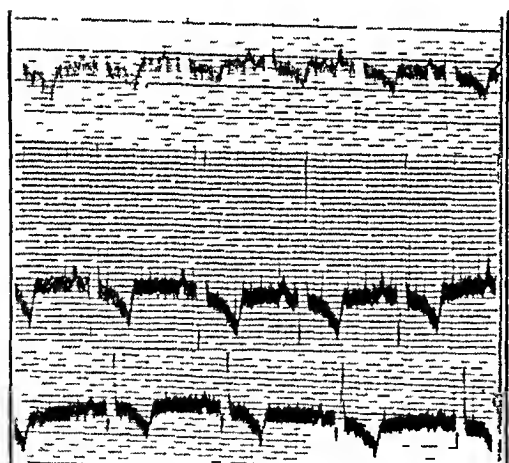


Fig 7

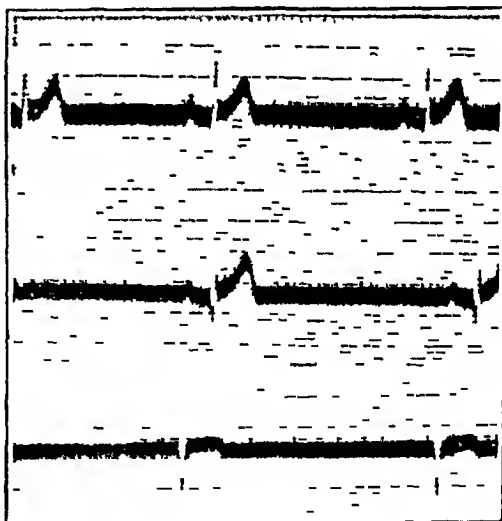


Fig 8

Fig 7—Dog 8 The record was taken thirty-eight days following the ligation of the ramus descendens anterior sinister. The T-wave is negative in all leads.

Fig 8—Dog 20 Electrocardiogram taken fifteen days following operation. An attempt was made to ligate the ramus circumflexus sinister. The ligature was around the vessel at necropsy, but the lumen was only partially occluded. The moderate left ventricular hypertrophy indicated by the electrocardiogram was verified at necropsy.

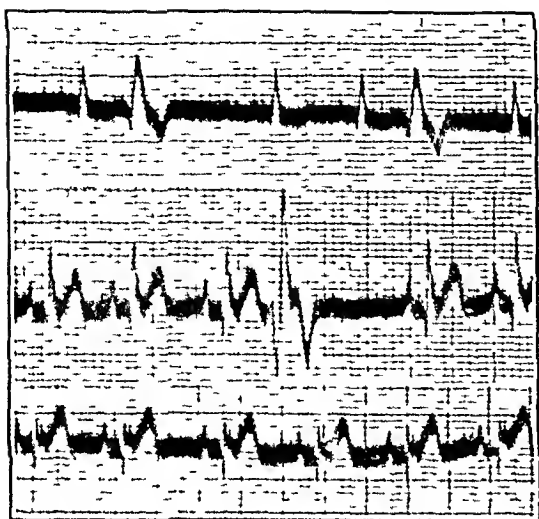


Fig. 9

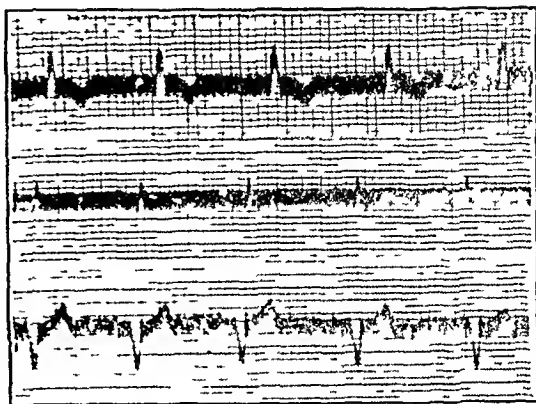


Fig. 10

Fig. 9—Dog 16 The record was made fifteen days following the ligation of the ramus circumflex sinister. The T-wave in Leads II and III has grown positive from a sharply negative phase. There are right ventricular premature contractions.

Fig. 10—Dog 16 Record taken thirty-five days following operation. The R-wave in Leads I and III is blunt. This was the only record of the series which showed this condition. The ramus circumflex sinister was ligated.

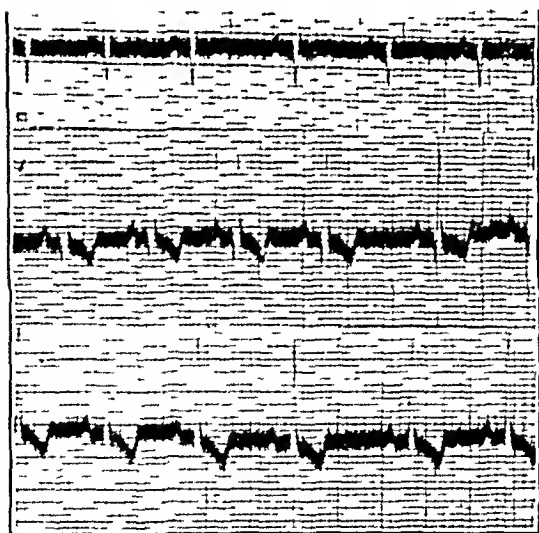


Fig. 11

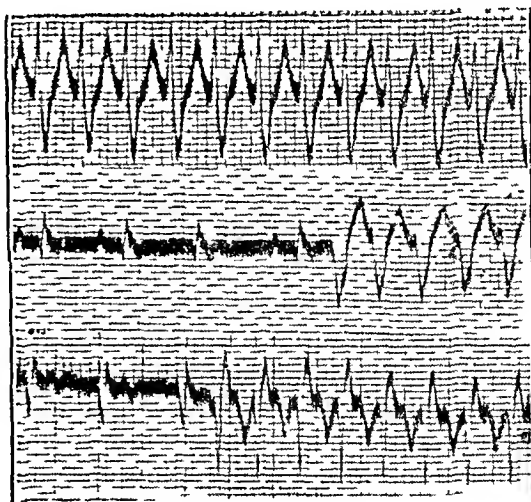


Fig. 12

Fig. 11—Dog 1 Record taken fifty-one days after ligation of the ramus descendens anterior sinister. The hypertrophy of the right ventricle indicated by the electrocardiogram was verified at necropsy.

Fig. 12—Dog 18 Record taken twenty-six days following the ligation of the ramus circumflex sinister. It shows the onset of two attacks of paroxysmal tachycardia.

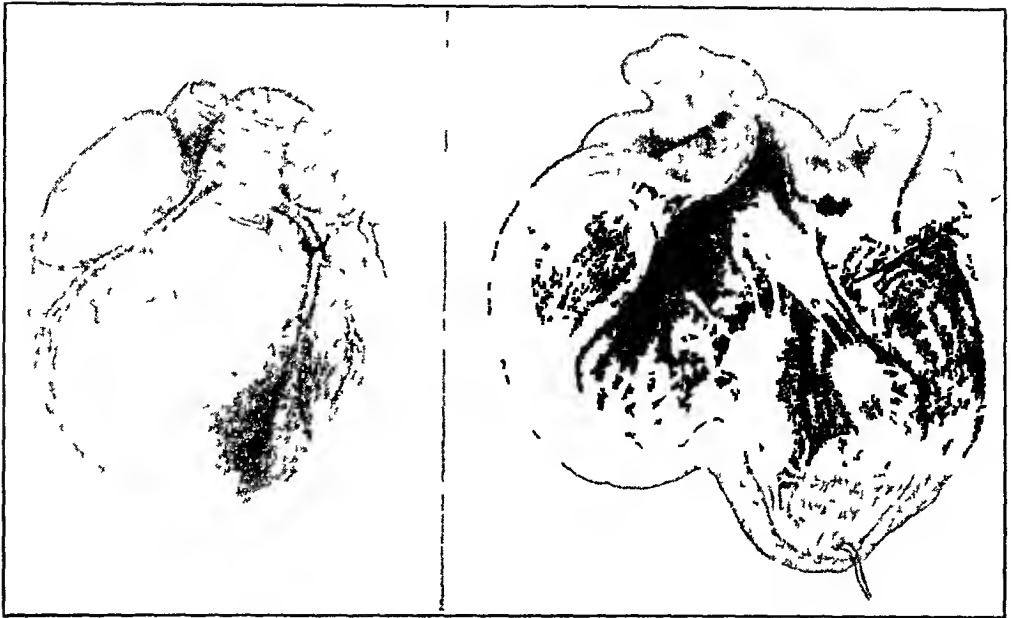


Fig 13—The ramus descendens anterior sinister is ligated. The lesion is typical of that resulting from the ligation of this artery. There is a thinning and fibrosis of the anterior wall of the left ventricle and septum especially marked at the apex.

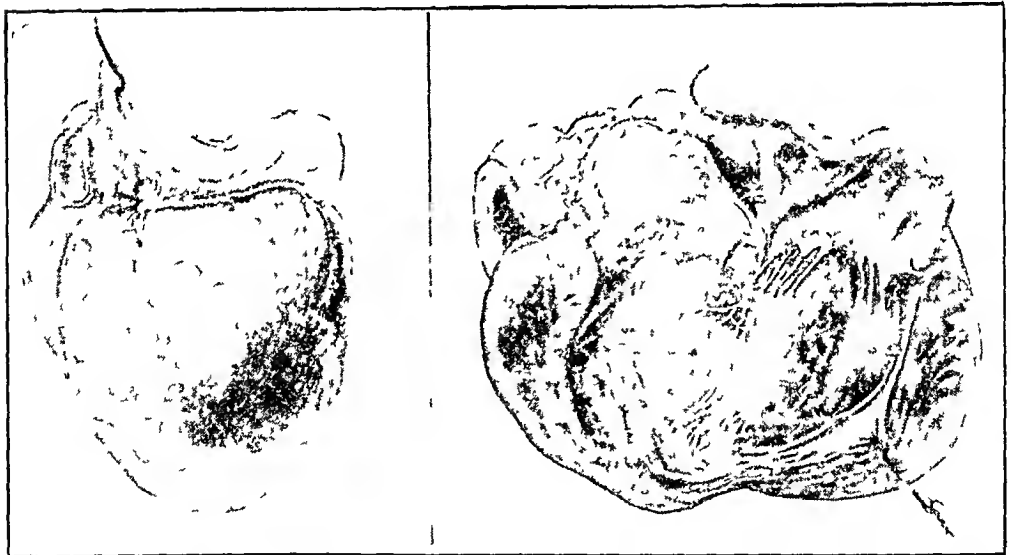


Fig 14—The ramus circumflexus sinister is ligated at the site of the ligature. The external change is a slight sinking and thinning of the posterior wall of the left ventricle. The endocardial change is a fibrosis of the posterior papillary muscle and in the immediate vicinity.

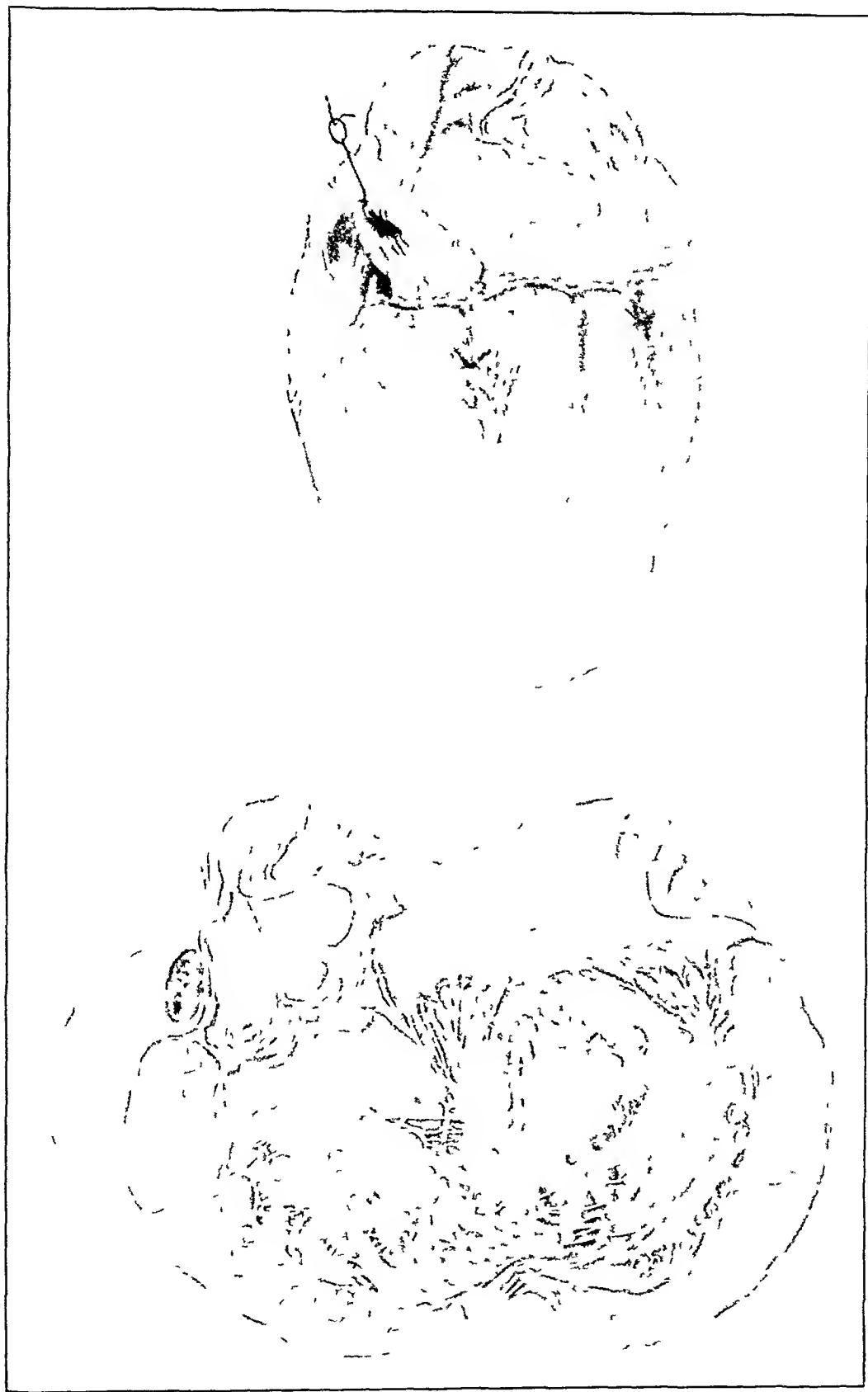


Fig 15—The first descending and the large posterior descending branches of the ramus circumflexus sinister were ligated. Illustration shows a fibrosis of the posterior papillary and a slight involvement of the anterior papillary muscle.

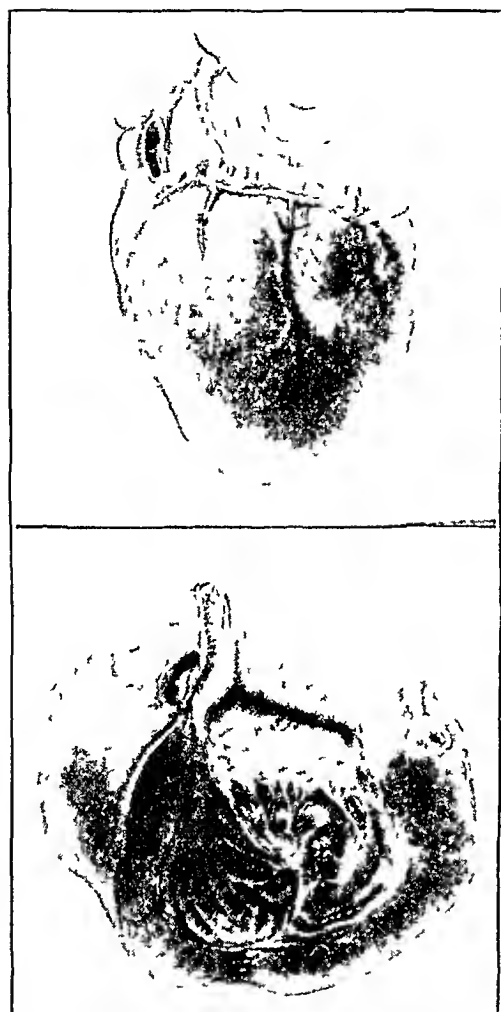


Fig 16—The second descending branch and the posterior portion of the ramus circumflexus sinister were ligated. The posterior papillary muscle has changed to a knot of fibrous tissue.

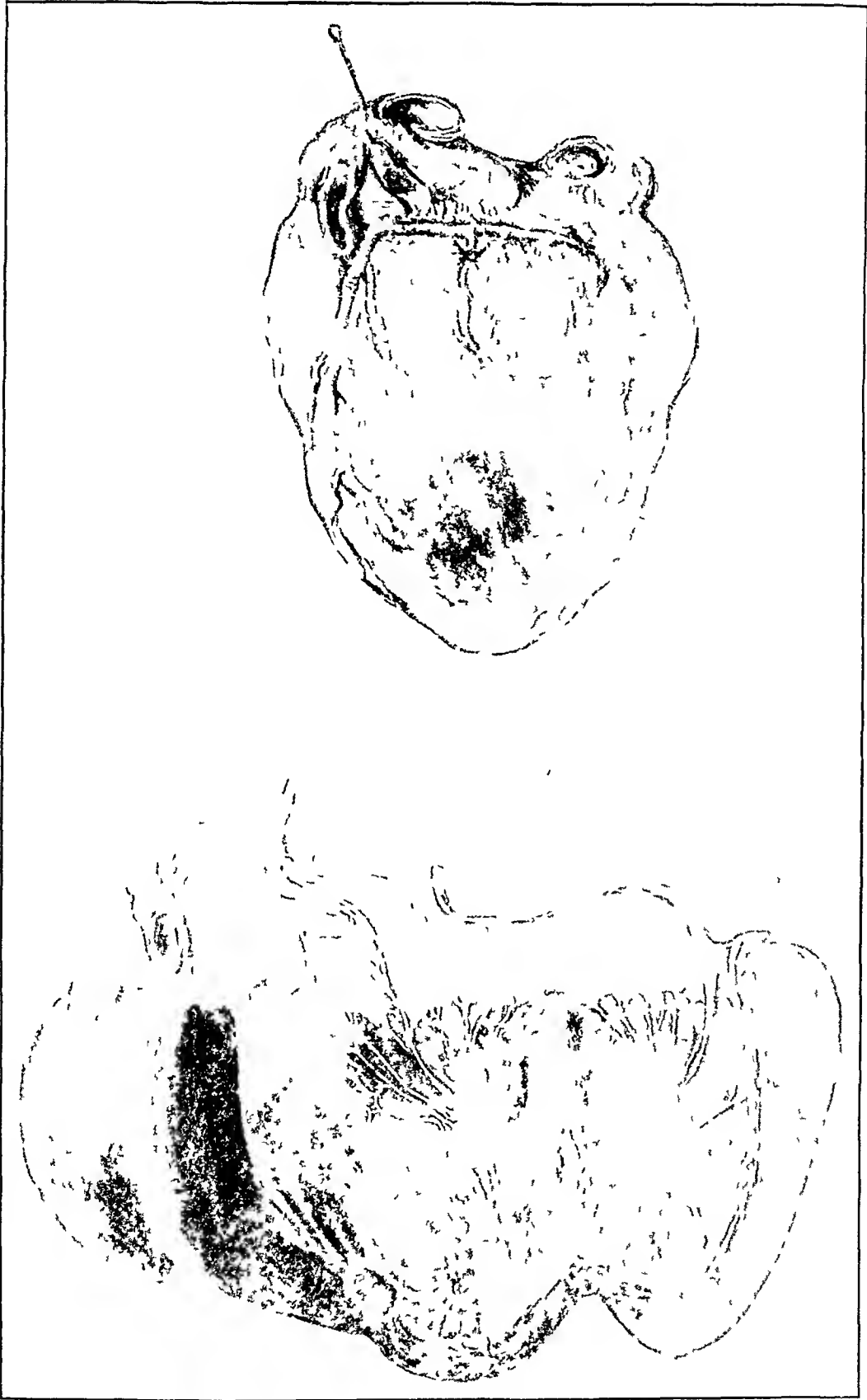


Fig 17—The anterior descending branch and the posterior descending portion of the ramus circumflexus sinister were ligated. The resulting endocardial lesion is a fibrosis of the posterior papillary muscle, showing the constancy of the lesion resulting from the ligation of these arteries.

Artery Ligated—In eleven dogs the ramus descendens anterior sinister was ligated from 1 to 2 cm from its origin. Dog 2 died within two minutes following the ligation. The ventricles suddenly went into fibrillation. It was afterward discovered that the dog had been previously used by Dr. Woodyatt for sugar injection. It is possible that before our operation there was disturbed function of the heart, as it was noted that the electrocardiogram taken before operation differed from the normal in that the T-wave was distinctly negative in all leads.

Ten dogs survived the operation, one died from sepsis on the eighth day. Dog 9 died on the seventeenth day with symptoms of failing myocardium. At necropsy the left ventricle was dilated and the anterior wall, including the apex, was very thin. The tenth dog of the series was found dead in the cage on the eighteenth day. No cause was found for death. Seven of the series remained in good condition until necropsy. They gained in weight, showed no evidence of fatigue on walking them to and from the electrocardiograph room, which was over one block distant. The time elapsing between operation and necropsy varied from eighteen to sixty-three days.

The ramus circumflexus sinister was ligated from 1 to 2 cm from its origin in fourteen dogs. Four animals died during the operation, ten awakened from anesthesia in fairly good condition, of these, four died the following night, six animals lived until necropsy time. They became fat and responded well to exercise. In fact, Dog 20 at one time fought several minutes with another dog without being much winded.

The right coronary artery was ligated 2 to 3 cm from its origin in eight dogs. Four died within five hours. Dog 30 died on the third day from sepsis. Dogs 31 and 32, which gradually grew thin and coughed and vomited frequently, were killed on the tenth and twentieth days respectively. At necropsy they were found to have bronchopneumonia. Dog 28 was killed on the twenty-eighth day, having completely recovered from the operation.

In eighteen dogs the ramus descendens anterior sinister and one or more branches of the ramus circumflexus sinister were ligated. Nine dogs died within twenty-four hours. Three died from infection in three, twelve and twenty-one days, respectively. Two grew thin and died from failing heart on the fifteenth and seventeenth days. The remaining four dogs were killed by anesthesia in from forty-two to eighty-nine days and necropsy held.

The first lateral branch of the ramus descendens anterior sinister and one or more of the branches of the left circumflex were tied off in sixteen dogs. The portion of the ramus circumflexus sinister was either the large anterior descending or the descending posterior branch. Six dogs died within twelve hours, one from hemorrhage from a sur-

gical blunder Two became infected and died on the second and tenth days The remaining eight were in fine condition There was no evidence of cardiac weakness

Electrocardiographic Study —The electrocardiographic curves taken before operation were fairly constant in conformation Figure 1 represents a type of curve which was encountered in the majority of cases The R wave in Lead I was always small, it was most prominent in Leads II and III The T-wave was small in all leads and not infrequently negative In those dogs in which the T-wave was inverted in all leads, the mortality seemed to be high within twenty-four hours following operation

Premature Contractions —Premature contractions were noted usually within a few minutes following the ligation The type depended on the portion of the heart involved When the right coronary artery or the circumflex branch of the left, both of which arteries supply blood liberally to the corresponding auricles and ventricles, was ligated, the premature contractions were both auricular and ventricular in type The ramus descendens anterior sinister supplies portions of the left ventricle and a limited area of the right Following the ligation of this artery left ventricular premature contractions and an occasional right were often noted

The number of premature contractions after one hour's time depended in a large degree on the artery ligated They were usually far more numerous following the occlusion of the right coronary artery and the circumflex branch of the left It was not uncommon to note many runs of three to five of these premature contractions This was especially noticeable on the day after operation, when at times there were runs of eight to ten After this, as a rule, they gradually decreased in number day by day After one week's time only an occasional one was seen in the electrocardiogram In some dogs, however — those in which the ramus circumflexus sinister had been ligated —premature contractions were observed in the electrocardiograms until death

Tachycardia —In four dogs after the ramus circumflexus sinister had been ligated, premature contractions of the left ventricular type were numerous within one hour's time There were many small runs of three to four, which gradually increased in number to from six to eight Finally a permanent tachycardia set in which ended in ventricular fibrillation and death Possibly this was the explanation of the death of many of the dogs that died within the first twenty-four hours In fact, one dog, just prior to death, which was twenty-four hours following operation, was observed with such tachycardia Dog 18 of this series, which had the ramus circumflexus sinister

ligated, had many premature contractions until the time of necropsy. On two occasions the animal was observed in paroxysms of tachycardia (Fig 12). These attacks were usually only a few minutes in duration. They could be produced by exercise and were checked by keeping the dog very quiet.

Ventricular Fibrillation—Ventricular fibrillation was invariably the outcome of a permanent tachycardia. Fibrillation of the ventricles was not, however, always preceded by tachycardia. In six instances the condition came on quite abruptly soon followed by the death of

TABLE 1—SUMMARY OF RESULTS FOLLOWING THE LIGATION OF THE RAMUS DESCENDENS ANTERIOR SINISTER

Dog Number	Date of Operation	Vessel Lig	Date of Necropsy	Duration of Life, Days	Cause of Death
1	1/20/17	Ramus descend ant sinister	3/12/17	51	Anesthetized
2	1/23/17	Ramus descend ant sinister	1/23/17	Died during operation	Ventricular fibrillation
3	1/24/17	Ramus descend ant sinister	3/26/17	63	Anesthetized
4	1/25/17	Ramus descend ant sinister	2/17/17	23	Anesthetized
5	1/26/17	Ramus descend ant sinister	2/ 3/17	8	Sepsis
6	1/27/17	Ramus descend ant sinister	2/17/17	21	Anesthetized
7	1/30/17	Ramus descend ant sinister	2/17/17	18	Anesthetized
8	1/31/17	Ramus descend ant sinister	3/24/17	53	Anesthetized
9	2/ 1/17	Ramus descend ant sinister	2/18/17	17	Anesthetized
10	2/ 3/17	Ramus descend ant sinister	2/21/17	18	Failing heart
11	2/ 6/17	Ramus descend ant sinister	3/12/17	33	Anesthetized

the animal. In one case the string of the galvanometer fluttered as in ventricular fibrillation, within one minute's time rhythmical contractions followed. No record was taken, for we felt confident that the ventricles were fibrillating and that the experiment would in a few seconds or minutes be finished by the complete stopping of the heart. The dog, however, recovered from the operation and was allowed to live seventy-four days.

In Dog 17 the auricles were fluttering within five minutes following the ligation of the ramus circumflexus sinister. An electrocardiogram taken five minutes later showed auricular fibrillation. This was followed shortly by ventricular fibrillation and death.

T-Wave—The changes in the T-wave following the ligation of any branch of the left coronary artery were among the most constant and most remarkable, and have not, we believe, been previously recorded by other observers. There was a fairly constant change from the strongly positive peak to a markedly negative, and then a slower return to the positive or iso-electric form. These changes were usually

TABLE 2—SUMMARY OF RESULTS FOLLOWING THE LIGATION OF THE RAMUS CIRCUMFLEXUS SINISTER

Dog No	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
12	2/ 7/17	Ramus circumflexus sinister	3/12/17	33	Anesthetized
13	2/ 9/17	Ramus circumflexus sinister	2/17/17	29	Anesthetized
14	2/12/17	Ramus circumflexus sinister	2/12/17	Died during operation	Acute dilatation of heart
15	2/12/17	Ramus circumflexus sinister	2/12/17	Died during operation	Tachycardia, acute dilatation of heart
16	2/14/17	Ramus circumflexus sinister	3/20/17	25	Anesthetized
17	2/15/17	Ramus circumflexus sinister	2/15/17	Died during operation	Ventricular fibrillation, acute dilatation of heart
18	2/17/17	Ramus circumflexus sinister	4/12/17	59	Anesthetized
19	2/21/17	Ramus circumflexus sinister	2/21/17	Died following night	?
20	2/21/17	Ramus circumflexus sinister	2/22/17	54	Anesthetized
21	2/22/17	Ramus circumflexus sinister	2/22/17	Died following night	Acute dilatation of heart
22	3/28/17	Ramus circumflexus sinister	3/28/17	25 minutes following operation	Tachycardia and ventricular fibrillation
23	3/ 3/17	Ramus circumflexus sinister	3/ 3/17	Died following night	Acute dilatation of heart
24	3/ 3/17	Ramus circumflexus sinister	4/14/17	41	Anesthetic
25	3/ 8/17	Ramus circumflexus sinister	3/ 9/17	Morning following	Acute dilatation of heart

as follows. Immediately following the ligation the T-wave became more prominent. As a rule, the height of this wave seemed to vary directly with the size of the branch of the left coronary artery ligated. Where a large vessel was occluded, the T-wave became very tall (Figs 2 and 3). In some instances it exceeded the height of the R-wave (Fig 3). On the other hand, when a small artery was ligated the increase in the height of the T-wave was very slight. Within twenty-four hours it became sharply negative (Fig 4). The larger

the artery the greater was the condition of negativity. This persisted for three or four days, after which it gradually grew less, until by the sixth or seventh day this peak again became positive in one lead, for example, Lead III. The duration of the negative T-wave seemed to depend on the size of the artery ligated. Where the artery was small the negative T lasted not more than from two to four days. While the T-wave usually became positive in Lead III first, followed successively by Lead II and I, occasionally the order was reversed, T in Lead I becoming positive first, followed by II and III.

TABLE 3—SUMMARY OF RESULTS FOLLOWING LIGATION OF THE RIGHT CORONARY ARTERY

Dog No	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
26	3/ 6/17	Right coronary artery	3/16/17	Died 6 hours following operation	Tachycardia, acute dilatation of heart
27	3/10/17	Right coronary artery	3/10/17	2 hours following oper	Tachycardia, acute dilatation of heart
28	3/14/17	Right coronary artery	3/ 4/17	3-4 hours following oper	Acute dilatation of heart
29	3/11/17	Right coronary artery	4/14/17	28	Anesthetized
30	3/17/17	Right coronary artery	3/20/17	3	Sepsis
31	3/21/17	Right coronary artery	3/31/17	10	Anesthetized, bronchopneumonia
32	3/24/17	Right coronary artery	4/13/17	20	Bronchopneumonia
33	3/27/17	Right coronary artery	3/22/17	Died following night	Acute dilatation of heart

The change of the T-wave from a negative to a positive phase was a gradual one, but progressed until the curve became markedly positive. This condition was usually observed from the second to the fourth week, and was frequently associated with a low voltage R-wave (Fig 9).

After the fourth week the T-wave again became iso-electric or negative in one or more leads and remained so until necropsy. In some cases this wave was very much below the base line (Fig 7). This was especially true after the ligation of large arteries, as the ramus descendens anterior and circumflex sinister.

Cardiac Hypertrophy—Those dogs in which the ramus descendens anterior sinister was ligated, after a period of from four to six weeks, gave an electrocardiogram typical of right ventricular preponderance. At necropsy the right ventricle was found hypertrophied (Fig 11). Those dogs in which small branches of the left coronary artery were

ligated, developed electrocardiograms typical of left-side preponderance, which was also verified at necropsy

Pathology—The pathologic lesions resulting from the ligation of the ramus descendens anterior were fairly constant in type, but varied widely in the extent of the involvement of the heart wall. This would suggest the possibility of a difference in the amount of collateral circulation. Externally there was invariably a triangular area of depression on the anterior surface of the heart along the line of the interventricular septum, involving the left ventricular wall (Fig 13). The base of this triangle was at the apex of the heart. This area was pale in color and soft or firm in consistency, depending on the age of the lesion. There was, however, often an area occupying the apex that was of soft consistency regardless of the age of the lesion and the amount of fibrosis in the surrounding tissue. In six hearts the ventricular wall at the apex was reduced almost to paper thickness, with beginning aneurism. This was observed in those hearts in which the lesion was extensive.

The endocardial degeneration was more extensive than the epicardial. The endocardium of the lower half of the septum, and the anterior left ventricular wall, including the apex and a small portion of the right ventricle adjoining the septum, were usually involved. Occasionally the base of the anterior papillary muscle was pinched off by the contraction of the fibrous tissue which later developed. The endocardium was pale or mottled in appearance, soft or firm in consistency, depending on the age of the lesion. In a few instances the lower portion of the septum was quite thin. Figure 13 illustrates a typical lesion resulting from the ligation of the ramus descendens anterior sinister.

The pathologic findings resulting from the ligation of the ramus circumflexus sinister were the most surprising, in that the external changes were comparatively small, in fact, in one instance, the only change noted was a small depression in the posterior wall of the left ventricle near the septum (Fig 14). On palpation, however, the posterior wall of the left ventricle was found to be somewhat thinned out. The endocardial changes were usually confined to the posterior wall of the left ventricle, involving especially the posterior papillary muscle (Fig 17).

The most extensive endocardial degeneration, as compared with that of the epicardium, was produced by the ligation of the various branches of the ramus circumflexus sinister. The ligation of the first descending branch of this artery generally resulted in fibrosis of the anterior papillary muscle, the ligation of the posterior descending portion of the ramus circumflexus sinister resulted in fibrosis of the posterior papillary muscle. So constant were these results that we could produce lesions of either one of these papillary muscles. In a large percentage of the cases the epicardial change was usually a

TABLE 4—SUMMARY OF RESULTS FOLLOWING THE LIGATION OF VARIOUS BRANCHES OF THE RAMUS DESCENDENS ANTERIOR AND CIRCUMFLEXUS SINISTER

Dog No	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
34	4/ 9/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	7/21/17	89	Anesthesia
35	4/11/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/ 4/17	Died 10 minutes after ligation	Acute dilatation of heart
36	4/12/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/12/17	Died following night	Acute dilatation of heart
37	4/14/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/14/17	Died 30 minutes following ligation	Ventricular fibrillation, acute dilatation of heart
38	4/16/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/17/17	Died 24 hours following operation	Acute dilatation of heart
39	4/18/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	7/ 5/17	78	Failing heart
40	4/21/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/21/17	Died 20 minutes following ligation	Ventricular fibrillation, acute dilatation of heart
41	4/23/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	8/15/17	83	Anesthesia
42	4/25/17	Lateral branch of ramus descendens anterior and posterior descending portion of circumflexus sinister	4/25/17	Died following night	Acute dilatation of heart
43	4/28/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	6/ 9/17	42	Anesthetized
44	4/30/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	5/12/17	5	Empyema
45	5/ 2/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	5/23/17	21	Empyema
46	5/14/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	5/14/17	Died following night	Acute dilatation of heart
47	5/11/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	5/16/17	Died following night	Acute dilatation of heart
48	5/19/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	7/ 1/17	61	Anesthesia

TABLE 4—SUMMARY OF THE RESULTS FOLLOWING THE LIGATION OF VARIOUS BRANCHES OF THE RAMUS DESCENDENS ANTERIOR AND CIRCUMFLEXUS SINISTER—*Continued*

Dog No	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
49	5/23/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	5/25/17	2½	Empyema
50	5/26/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	5/30/17	4	Failing heart
51	5/30/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	6/ 6/17	6	Meningitis
52	6/ 2/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	8/21/17	49	Anesthesia
53	6/ 6/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	6/14/17	8	Sepsis
54	6/23/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	6/23/17	Died 1 hour after operation	Acute dilatation of heart
55	6/25/17	Lateral branch of ramus descendens anterior and posterior portion of ramus circumflexus sinister	7/21/17	26	Anesthesia
56	6/27/17	Lateral branch of ramus descendens anterior and posterior portion of ramus circumflexus sinister	6/27/17	Died following night	Acute dilatation of heart
57	6/30/17	Anterior descending branch and the posterior portion of ramus circumflexus sinister	7/ 6/17	7	Sepsis
58	7/ 7/17	Anterior descending branch and the posterior portion of ramus circumflexus sinister	10/ 6/17	91	Anesthetized
59	7/12/17	Two lateral branches of ramus descendens anterior and descending portion of ramus circumflexus sinister	7/12/17	1 hour following operation	Tachycardia and acute dilatation of the heart
60	7/14/17	Two lateral branches of ramus descendens anterior and descending portion of ramus circumflexus sinister	7/14/17	20 minutes following operation	Hemorrhage from surgical error
61	7/16/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	10/ 6/17	82	Anesthetized

TABLE 4—SUMMARY OF RESULTS FOLLOWING THE LIGATION OF VARIOUS BRANCHES OF THE RAMUS DESCENDENS ANTERIOR AND CIRCUMFLEXUS SINISTER—(Continued)

Dog No	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
62	7/18/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	9/30/17	74	Anesthetized
63	7/20/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	10/6/17	77	Anesthetized
64	7/26/17	First lateral branch of ramus descendens anterior sinister and first descending branch of ramus circumflexus sinister	7/28/17	2	Sepsis
65	7/28/17	Two lateral branches of ramus descendens anterior and posterior portion of circumflexus sinister	10/6/17	70	Anesthetized
66	7/29/17	Two lateral branches of ramus descendens anterior and posterior portion of circumflexus sinister	7/29/17	Died following night	Acute dilatation of heart

depression less than the size of a five cent piece at the site of the ligation (Figs 15 and 16)

The lesion resulting from the ligation of the right coronary artery was confined to the lateral and anterior surface of the right ventricle. It was usually about the size of a silver dollar, being more extensive on the endocardial than epicardial side. In addition, there were small areas of fibrosis from 1 to 5 mm in diameter disseminated throughout the right auricle.

Microscopic Findings—The microscopic changes were those which have many times been described as resulting from experimental or clinical occlusion. Within twenty-four hours from the time of operation there was an infiltration of round cells and red blood corpuscles within and between the muscle cells. The protoplasm of the cells stained less deeply and the nuclei were paler. After one week fibrous tissue cells had already begun to form, and the muscle cells were in a more advanced stage of degeneration. The fibrous tissue gradually replaced the degenerated cells until by the end of three weeks the fibrosis was fairly extensive.

DISCUSSION

Mortality—In general the mortality in our series compares closely with that of late experimenters, where ether is used as an anesthetic, where artificial respiration is kept up, and where a rapid aseptic sur-

gical operation is done. The earlier experimenters, as Cohnheim, it will be remembered, had a much higher mortality, and even Porter,¹ whose results were much more favorable because of better technic, lost more dogs than later investigators. The mortality in our series following the ligation of the ramus descendens anterior sinister was 9 per cent. Porter's was 64 per cent. Miller and Matthews² had no deaths following the ligation of this artery. Where in addition we ligated one or more small branches of the ramus circumflexus sinister, the mortality was increased to 50 per cent. This was about the same as that from the ligation of either the main trunk of the ramus circumflexus sinister or the right coronary artery, which was 57 per cent and 54 per cent, respectively. Miller and Matthews had a mortality of only 8.7 per cent from the ligation of the ramus circumflexus sinister. The difference between our figures and those obtained by Miller and Matthews is, perhaps, explained because we used no digitalis or allied drugs prior or subsequent to ligation. These investigators feel certain that intravenous administration of strophanthin decreased their mortality.

The mortality following the ligation of the first lateral branch of the ramus descendens anterior and either the large anterior or posterior descending branch of the ramus circumflexus sinister was 37½ per cent. These figures approached those obtained from the ligation of the ramus circumflexus sinister or the right coronary artery, yet the area supplied with blood by the last named arteries far exceeds that supplied by the former. Even though the area supplied with blood in the former is less, the papillary muscles are involved, which perhaps may be the explanation for the high death rate.

Pathology—One fact, strikingly brought out, was that where a lesion was brought about by ligation of the left coronary artery, the softening or fibrosis involved to a much greater extent the endocardial and subendocardial structures than the subpericardial or the body proper of the myocardium. This was true in two cases in man with coronary artery occlusion which we had the opportunity of observing while the work was going on. Oppenheimer and Rothschild³ have recently called attention to this condition in sclerosis of the coronary arteries. Eight of their cases had occlusion of the ramus descendens anterior of the left coronary artery. While confirming their observa-

1 Porter. Results of Ligation of the Coronary Arteries, *Jour. Physiol.*, 1894, **15**, 121.

2 Miller, J. L., and Matthews, S. A. Effects on the Heart of Experimental Obstruction of the Left Coronary Artery, *THE ARCHIVES INT. MED.*, 1909, **3**, 476.

3 Oppenheimer and Rothschild. Electrocardiographic Changes Associated with Myocardial Involvement with Special Reference to Prognosis, *Jour. Am. Med. Assn.*, 1917, **69**, 429.

tions as to the location of the pathologic changes, we are not prepared to accept in its entirety their "arborization block" explanation of the electrocardiographic phenomena seen in such cases. We feel that further study of this feature is necessary.

Anastomosis—The question of an anastomosis between the right and left coronary arteries has been often discussed. Our observations on these dogs lead us to the belief that while the degree of anastomosis is variable, there must often be a fairly free communication between the branches of the right and left arteries or between the smaller branches of the same artery. Otherwise it is difficult to explain the survival of dogs where extensive ligation has been made, the variations in extent of the lesions produced by the obstruction of the same vessel and the comparatively small size of the lesion which frequently results from the occlusion of a large artery.

The same conclusions, we believe, can be drawn with regard to the anastomosis of the coronary arteries in man. In a case that we recently studied, although the ramus descendens anterior sinister and the large anterior descending branch of the circumflexus sinister were completely occluded by thrombi, the only external change was a small depression the size of a fifty cent piece on the anterior wall of the left ventricle. Similar observations have been made by Thorel, Chiari, Merkel, Dock, Herrick⁴ and others, in which a fairly rich collateral circulation, capable of functioning, must be assumed to exist as an explanation of the survival of the patient with such a comparatively small area of myocardial involvement after an extensive obstruction of a larger vessel.

Electrocardiograph Study—The various types of premature contractions, the appearing of these in runs of three to eight, with an occasional onset of tachycardia, have been recorded by Lewis⁵ in his work on tachycardia produced by the ligation of the coronary arteries. He observed tachycardia very frequently following the ligation of the right coronary artery, and in one instance following the ligation of the ramus descendens anterior. The majority of these tachycardias described by Lewis did not develop until after one hour subsequent to the ligation. He concluded that even a large number of his dogs would have developed the normal rhythm if he had observed them over a longer period of time. Six out of ten of his animals regained the normal rhythm after developing tachycardia, the remaining four went into ventricular fibrillation and died. In our series, four dogs in which the ramus circumflexus sinister was ligated, developed, within forty minutes, tachycardia which ended in ventricular fibrillation and death.

4 Herrick, J. B. Clinical Features of Sudden Obstruction of the Coronary Arteries, Jour Am Med Assn, 1912, **59**, 2015.

5 Lewis. The Experimental Production of Paroxysmal Tachycardia and the Effect of Ligation of the Coronary Arteries, Heart, 1909-1910, **1**, 43.

Dog 18, in which the ramus circumflexus sinister was ligated, was observed on two different occasions in an attack of tachycardia weeks following the operation. The animal was in fine condition at the necropsy which was fifty-nine days from the time of ligation. We have previously stated that the frequency with which paroxysmal tachycardia developed subsequent to the ligation of the ramus circumflexus sinister and the right coronary artery may explain the death of many of these animals the night following the operation. This supposition is made even more plausible by the fact that we observed one animal die in one of these attacks twenty-four hours following operation.

Ventricular fibrillation was observed in six cases. In four instances this abnormal rhythm was preceded by tachycardia and in the remaining two by auricular fibrillation and auricular flutter. Ventricular fibrillation in the dog invariably ended in death. We observed one case in which we believe the normal rhythm was reestablished. Recovery in small animals is very common. Gunn⁶ observed this feature in rats. MacWilliams⁷ reported recovery in dogs, and recently Robinson and Bredeck⁸ have described a case in man in which the normal rhythm returned after a ventricular fibrillation had been well established.

The changes in the T-wave we have already described. If confirmed, these observations may be of considerable value from a diagnostic point of view, at least as concerns the left coronary artery. The early exaggeration of the T-wave, its marked negative drop below the line within twenty-four hours and its more gradual return to its positive position and its final iso-electric or negative location were so characteristic in dogs watched for several days, that similar changes in the wave in man might reasonably be supposed to be due to similar lesions. In fact, one case in man, which will be reported later, was observed in which a clinical diagnosis of coronary thrombosis was made by Dr. James B. Herrick which was verified later at necropsy. The T-wave of the electrocardiogram of the patient ran a course similar to that of the dogs previously described. In other cases believed to be coronary thrombosis similar changes in the electrocardiogram have been seen but no verification of the diagnosis has been made, the patients either living or no necropsy having been obtained.

122 South Michigan Avenue

It is a great pleasure to acknowledge my indebtedness to Dr. James B. Herrick for his many suggestions and to Dr. E. M. Miller who assisted in the first thirty-three operations.

6 Gunn. Ventricular Fibrillation in Rats' Hearts, *Heart*, 1913-1914, 5, 1

7 MacWilliams. *Jour. of Physiol.*, 1887, 8, 296

8 Robinson and Bredeck. Ventricular Fibrillation in Man with Cardiac Recovery, *THE ARCHIVES INT. MED.*, 1917, 20, 225

THE CLINICAL REGISTRATION OF CARDIAC MURMURS BY THE DIRECT METHOD[†]

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I INTRODUCTION

The need of a simple yet efficient device for recording heart sounds, in conjunction with pulse tracings and electrocardiograms, caused Dean and the writer to experiment extensively with various forms of apparatus designed to record heart sounds directly. This experimental work, together with a careful study of published records, convinced us that at the time no so-called "direct method" of sound registration was satisfactory for clinical use. Further experimentation then led us to modify the Frank segment capsule so as to render it more sensitive and protected from extraneous sounds.¹ A mechanical diagram of the apparatus, as improved in minor details, is drawn to scale in Figure 1.

By this apparatus satisfactory records of normal heart sounds can be obtained provided certain simple principles are followed. The clinical adaptability of these capsules could not be guaranteed, however, until their ability to record cardiac murmurs was established. Such a test under hospital conditions was made possible during the months of January and February, 1917, in the wards of the Second Medical Division of Bellevue Hospital through the courtesy and cooperation of Drs. Coleman, Du Bois, Goodridge, Meara, Miller and Niles. For this purpose the capsules were mounted on a table which could be wheeled to the bedside in the wards. To the collection of phonocardiograms thus recorded simultaneously with optical records of the jugular, subclavian or radial pulse were added others from cases kindly diagnosed and referred to the physiological laboratory from the Cornell Medical Dispensary by Dr. Sheldon. The records published in this paper as typical samples of different types of murmurs are offered as evidence that in the majority of cardiac diseases the recognized auscultatory signs can be satisfactorily recorded by this single method.

* Submitted for publication Feb 7, 1918

* From the Physiological Laboratory, Cornell University Medical College, and the Second Medical Division, Bellevue Hospital

1 Wiggers, Carl J., and Dean, Archie, Jr. Principles and Practice of Registering Heart Sounds by Direct Methods, *Am Jour Med Sc*, 1917, **153**, 666
Ibid, The Nature and Time Relations of the Fundamental Heart Sounds, *Am Jour Physiol*, 1917, **42**, 476

II THE DIFFERENTIATION OF SOUNDS AND MURMURS IN PHONOCARDIOGRAMS

Sounds and murmurs present distinct differences in quality to the ear. In phonocardiograms both are composed of a sequence of vibrations, irregular as regards both their individual amplitudes and periods. It is therefore impossible to differentiate sounds from murmurs on a basis of the regularity, frequency or amplitude of their component vibrations. What, then, are the criteria that differentiate murmurs from sounds in phonocardiograms? Previous investigators have emphasized the importance of establishing the time relations of the vibration groups to other records, such as the pulse or electrocardiogram. This is always most helpful and, when the sounds are very abnormal, often absolutely necessary. Normal sounds have, however, a characteristic grouping of vibrations which though it varies in dif-

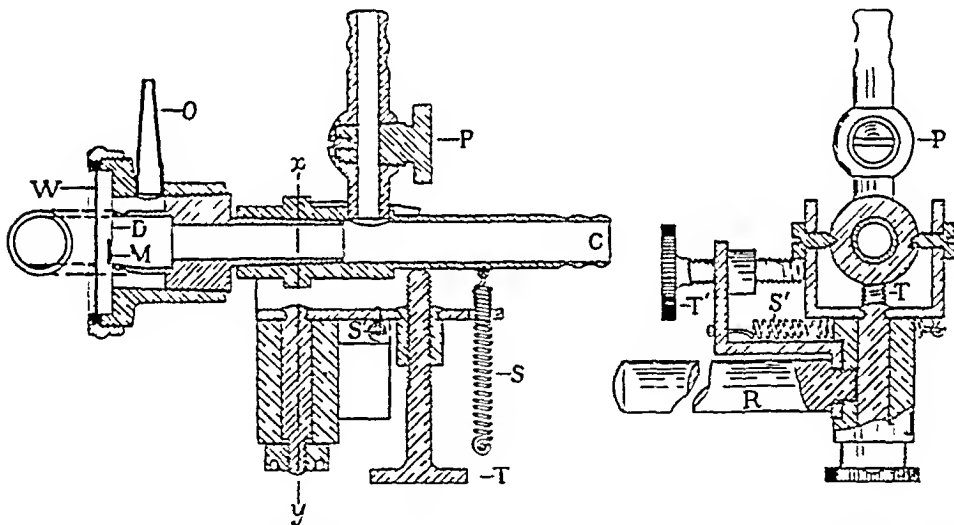


Fig 1—Mechanical diagrams of heart-sound apparatus. Figure to right, section through X-Y, scale two thirds actual size. C, tube connecting with stethoscope bell, P, stopcock regulating opening in system, D, rubber film covering segment capsule, M, mirror, O, conical vent communicating with exterior to equalize pressure in chamber, S, S', springs, T, screw for adjusting reflected beam of light horizontally, T', screw for adjusting same laterally, R, rod for clamping apparatus to rigid support, W, glass window for protecting membrane from extraneous vibrations. (Kindly drawn by G F Soderstrom.)

ferent individuals, the eye soon learns to distinguish as a sound complex. The characteristics of sounds are far more difficult to describe than to visualize. Two phonocardiograms showing such normal sounds are shown in Figure 2. In B the second sound was somewhat accentuated and, therefore, relative to the first sound, of larger amplitude. The first sound (I) is of longer duration than the second (II). Both sounds reach a maximum amplitude rapidly and, after a swift decrescendo, stop abruptly. If there is any single characteristic that most unfailingly differentiates sounds from murmurs in phonocardiograms

it is the short duration and abrupt cessation of the "sound vibrations" as contrasted with the more prolonged nature of the murmurs. This is in entire accord with our conception of the causes of sounds and murmurs. Neither are sounds in a physical sense but belong to the category of "noises." The so-called "heart sounds" owe their peculiar auditory quality to the fact that vibrations of irregular sequence and amplitude are suddenly produced by the action of a temporary force; hence the damped vibrations soon cease. Murmurs, on the other hand, owe their auditory quality to the fact that vibrations of an irregular nature are produced by a continued force, usually though not always of less intensity than that responsible for sound vibrations.

In order to analyze phonocardiograms it is essential first to recognize the "sound complexes" and then to refer the remaining vibrations

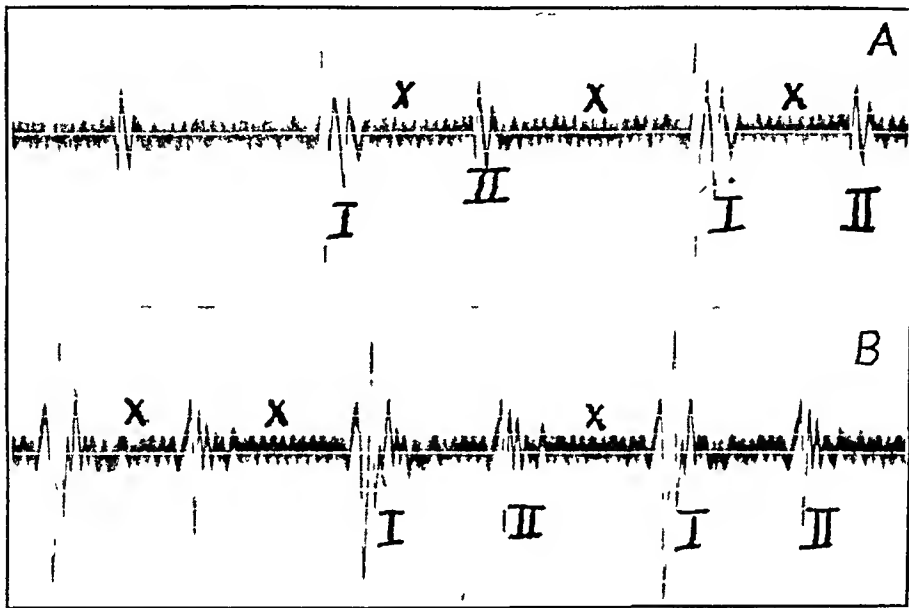


Fig 2—Phonocardiogram showing normal heart sounds. In B the second sound is accentuated.

to murmurs. In doing this it is necessary, however, to discount certain unavoidable, accidental vibrations, much as in microscopic diagnosis we disregard artefacts of fixing and staining, or as in auscultation the ear is trained to disregard adventitious sounds. In the phonocardiograms of Figure 2 there may be observed between the sounds small vibrations (X) due to such extracardiac vibrations. These are sometimes somewhat larger and must not be confused with murmurs. In cases in which marked dyspnea is present or other pulmonary sounds are pronounced, they may occasionally obscure murmurs entirely. This is also the case when the murmurs are very soft and the accidental vibrations no greater than normal.

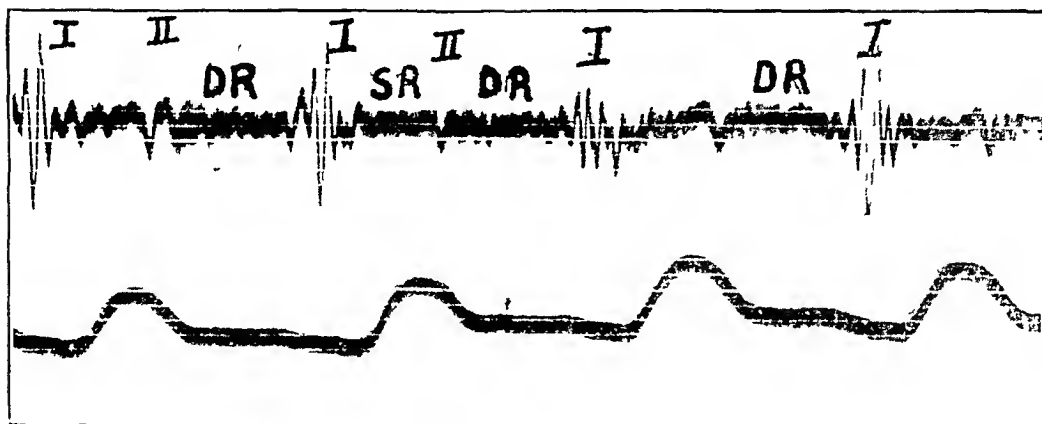


Fig 3—Phonocardiogram showing, in addition to heart sounds, systolic friction rub (SR) and diastolic friction rub (DR) Lower record, radial pulse

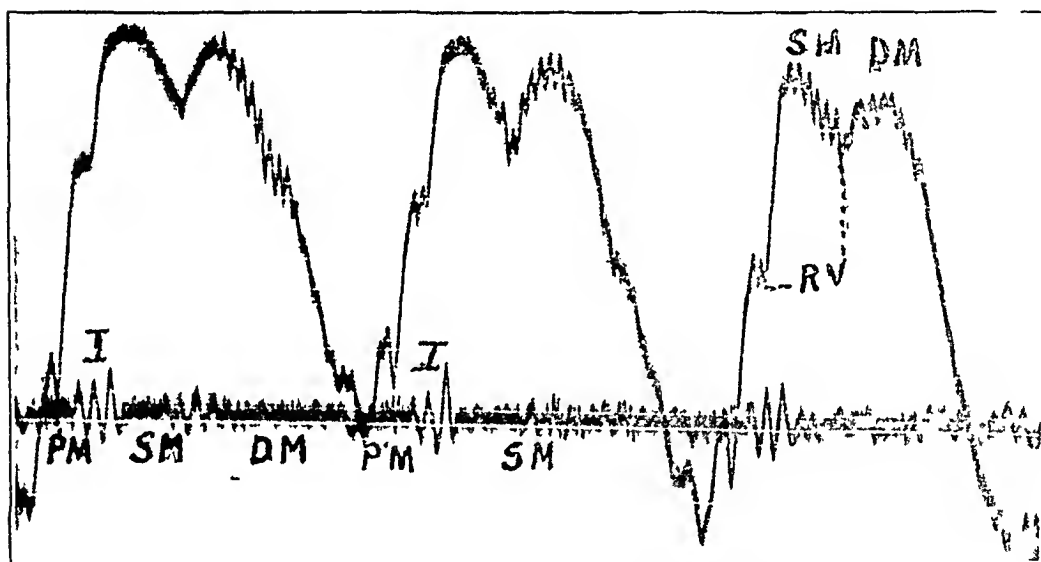


Fig 4—Phonocardiogram and jugular tracings from case of aortic insufficiency Phonocardiogram shows, in addition to first sound (I), presystolic (PM), systolic (SM), and diastolic (DM) murmurs Systolic and diastolic murmurs are also shown superimposed on the regurgitant wave (RV) of the jugular tracing

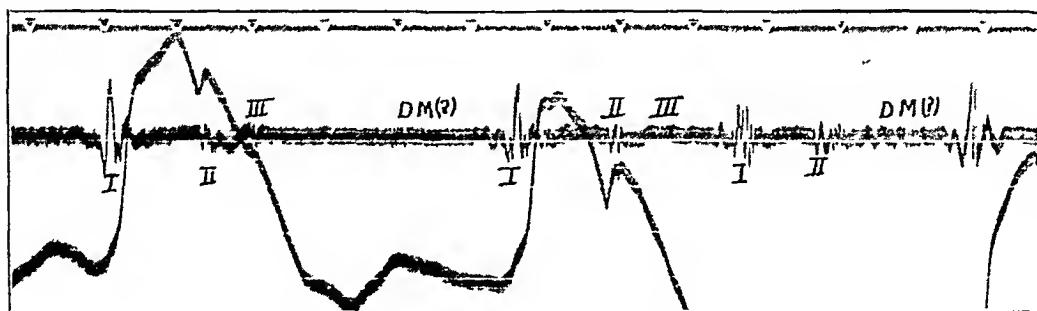


Fig 5—Phonocardiogram and subclavian pulse from case of auricular fibrillation Phonocardiogram shows in addition to heart sounds, a diastolic murmur Systolic murmur heard on auscultation was not recorded

III DESCRIPTION OF PHONOCARDIOGRAMS IN DIFFERENT
CARDIAC LESIONS *

CASE J-2—Mr W D *Acute Pericarditis* Systolic and diastolic friction rub best heard over the right border of the sternum but distinctly audible at the apex (Dr Coleman)

From the areas where sounds were heard with greatest intensity by the ear, no satisfactory records either of the heart sounds or the friction rub could be obtained Over the apex, as shown in Figure 3, the first sound (I) is apparently normal, varying in amplitude with inspiration and expiration as is normal The second sound (II) is barely indicated The periods of systole (I to II) and diastole (II to I) are filled with a regular series of vibrations of high frequency (SR, DR), quite different from the accidental vibrations usually present They are present very clearly during all the periods of diastole, but are only occasionally present as distinct vibrations during systole The second cycle of Figure 3 shows both the systole (SR) and diastole friction rub (DR) clearly

CASE J-3—Mrs E G *Aortic Insufficiency* Rough diastolic murmur over aortic area transmitted across the sternum, loudest at the level of the third rib Presystolic (Flint) and systolic murmurs over apex Systolic and diastolic murmur audible in supraclavicular region Radial pulse gives tactile impression of a collapsing pulse (Dr Miller)

Phonocardiograms taken from the apex region (Fig 4) show the vibrations of the first sound (I) clearly They are abnormal in character The second sound is entirely absent Preceding the first sound there occurs regularly a group of presystolic vibrations (P) corresponding to the presystolic murmur heard on auscultation Following the first sound and filling the period of systole are a group of vibrations (S) which probably correspond to the systolic murmur but could not be so interpreted without auscultatory aid and the fact that the venous pulse contains "regurgitant waves" (RV) (Niles and Wiggers²) with systolic vibrations (SM) superimposed The second sound is replaced by a series of vibrations which extend into diastole (DM) and correspond to the diastolic murmur heard best further to the right They are also superimposed on the V wave of the venous tracing (DM)

CASE J-4—Mr E D *Auricular fibrillation Mitral lesion* Systolic murmur at the apex (Drs Du Bois and Barr)

* All records reproduced in this article were reduced in size, consequently the smaller vibrations in some records will appear more clearly if examined with a magnifying hand lens

2 Niles, Walter L, and Wiggers, Carl J The Details of the Photographically Recorded Venous Pulse in Auricular Fibrillation, and the Significance of the Diastolic Waves of the Venous Pulse in Auricular Fibrillation, Jour Exper Med, 1917, 25, 1

Phonocardiograms taken from the apex (Fig 5) show vibrations typical of a first and second sound (I, II) and in the long cycles a third sound (III) although the latter was not heard on auscultation. The character of the first sound varies from one cycle to another, which is typical in auricular fibrillation or any other form of irregular-

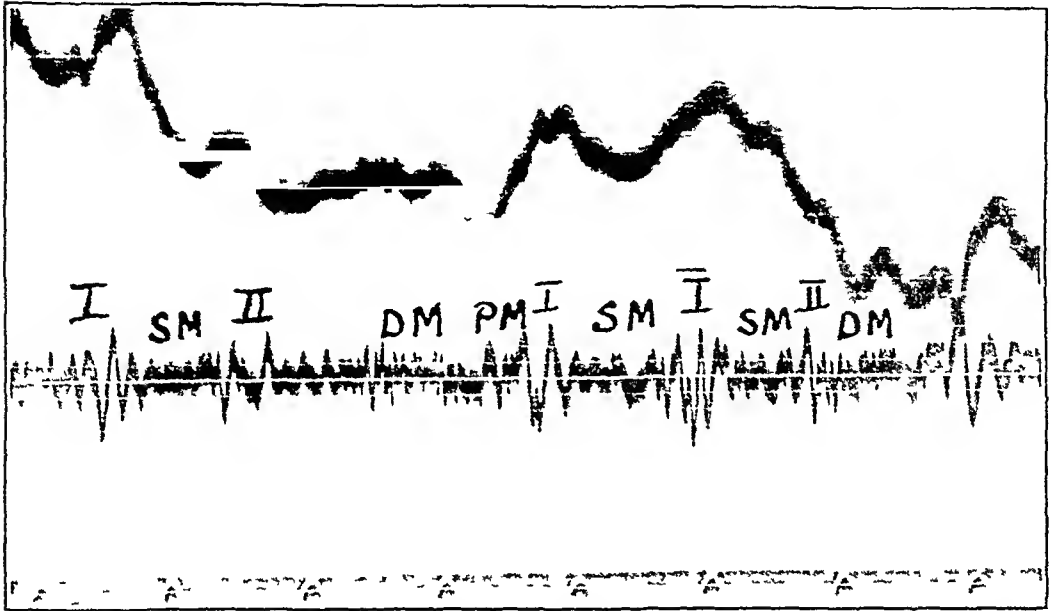


Fig 6—Phonocardiogram taken from same patient as Figure 6 showing, in addition to first and second sounds a presystolic (PM), systolic (SM) and diastolic (DM) murmur. Upper tracing, jugular pulse.

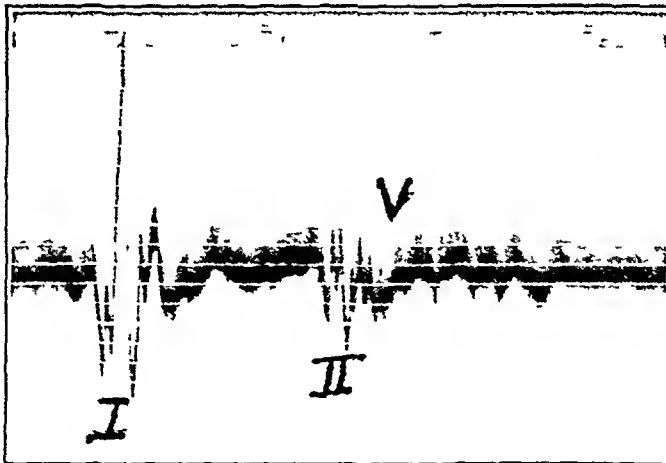


Fig 7—Phonocardiogram recorded from case of mitral stenosis. Note peculiar character of first sound and series of vibrations (V) following second sound, indicating a diastolic murmur which could not be heard on auscultation.

ity of the ventricle. Aside from these sounds, vibrations which may be doubtfully referred to as a diastolic murmur are present (DM?). No vibrations due to a systolic murmur distinctly heard on auscultation.

tion are present in this record. By moving the receiving cup slightly to the right a phonocardiogram was obtained (Fig 6) that showed a distinct systolic murmur. Its character and constancy varied from beat to beat, sometimes following a distinct first sound, as shown in Figure 6, occasionally practically replacing the first sound, as shown in unpublished records. A diastolic murmur is indubitably present in this record, although no note of such a murmur was made at the time of auscultation. The vibrations, in some cycles at least, fill the entire period of diastole right up to the next first sound, so that a presystolic murmur (PM) can be said to exist.

CASE J-5—Mr J K *Mitral stenosis*. Presystolic murmur having a peculiar metallic quality and terminating in a sharp first sound. Systolic shock at the apex, but no thrill (Dr Niles).

The phonocardiograms recorded (Fig 7) show a very pronounced series of vibrations quite different from that recorded normally for the

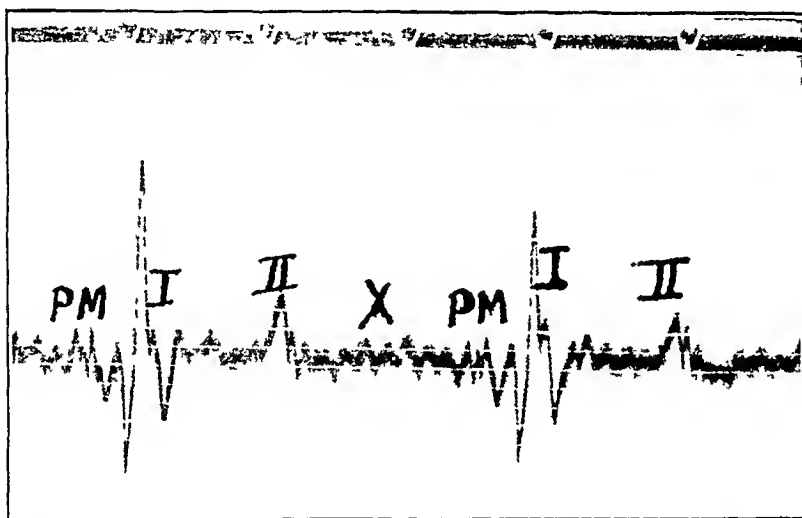


Fig 8—Phonocardiogram from case of mitral stenosis, showing, in addition to first and second sounds, a presystolic murmur (PM)

first sound (I). The large wave is evidently indicative of the shock felt on palpation and the sharp quality heard on auscultation. No evidence of the presystolic murmur is indicated. Unfortunately, no other record was obtained, owing to the fact that the patient left the hospital.

The second sound is peculiar in character and followed by a series of vibrations (V) that might indicate a short diastolic murmur. Careful reauscultation failed to elicit such a murmur, however (Dr Niles).

CASE J-6—Mrs E M *Mitral stenosis*. Loud presystolic murmur over the apex (Dr Niles).

Many phonocardiograms were taken but all showed nothing except an increased amplitude of the first sound and the peculiar characteristics apparently associated with mitral stenosis. Finally a record was obtained (Fig 8) that gave clear indication of such a presystolic murmur (PM) running into the vibration composing the first sound

CASE J-7—Mr A F *Mitral lesions* Diffuse apex pulsation, rough presystolic murmur at the apex and over the pulmonary area (Dr Niles)

Phonocardiograms taken from the apex area (Fig 9) show a series of presystolic variations (PM) separated by a short interval from the first sound (I). The vibrations composing this sound are of approxi-

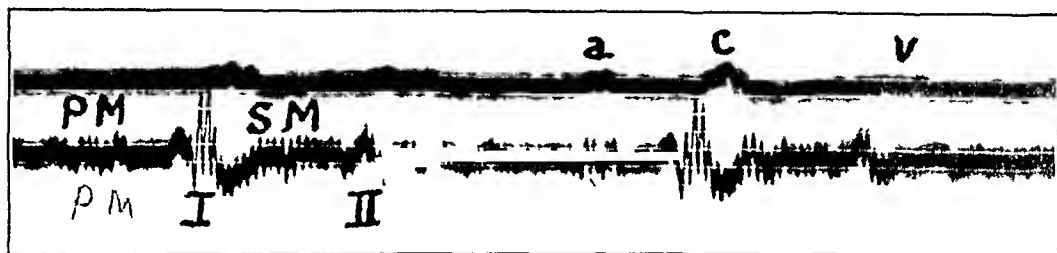


Fig 9—Phonocardiogram and jugular pulse found in case with mitral lesions, showing, in addition to first and second sounds, a presystolic murmur (PM) separated from the first sound and a systolic murmur (SM) continuing throughout systole

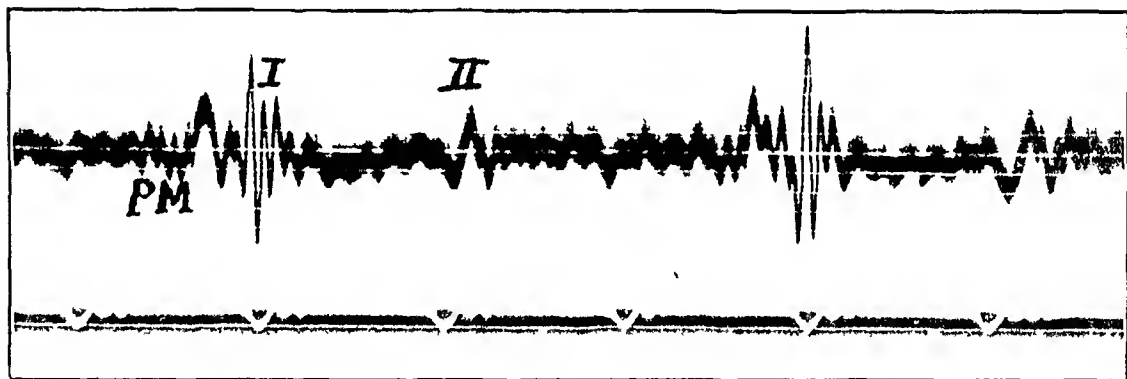


Fig 10—Phonocardiogram from a case of mitral stenosis, showing presystolic murmur (PM) merging with the first sound

mately the same period and are immediately followed by variations responsible for the systolic murmur (SM). The second sound (II) is barely indicated and the period of diastole is free from murmur vibrations.

CASE J-8—Mr J B *Mitral stenosis* Loud, long presystolic murmur ending in a sharp first sound heard best at the apex (Dr Du Bois)

Phonocardiograms taken from the apex region (Fig 10) showed repeatedly a clearly defined set of presystolic vibrations (PM) ending abruptly in the vibration of the first sound (I).

CASE J-9—Mrs G N *Decompensation of heart Possible aortic insufficiency or aortic dilatation* Systolic murmur at the apex Musical diastolic murmur at the left second intercostal space and over the sternum (Drs Niles and Miller)

From the area over the aortic region and over the sternum phonocardiograms, such as shown in Figure 11, were recorded The character of the first sound (I) differs appreciably from normal and varies

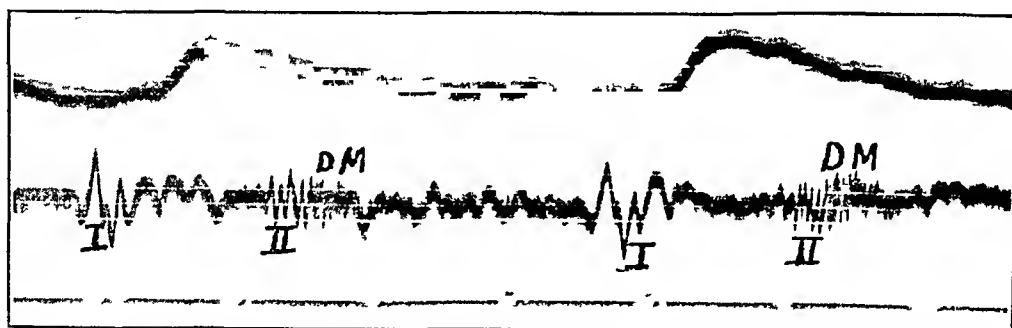


Fig 11—Phonocardiogram and radial pulse from a case of cardiac decompensation Probably aortic insufficiency Phonocardiogram shows a short, musical diastolic murmur following the second sound

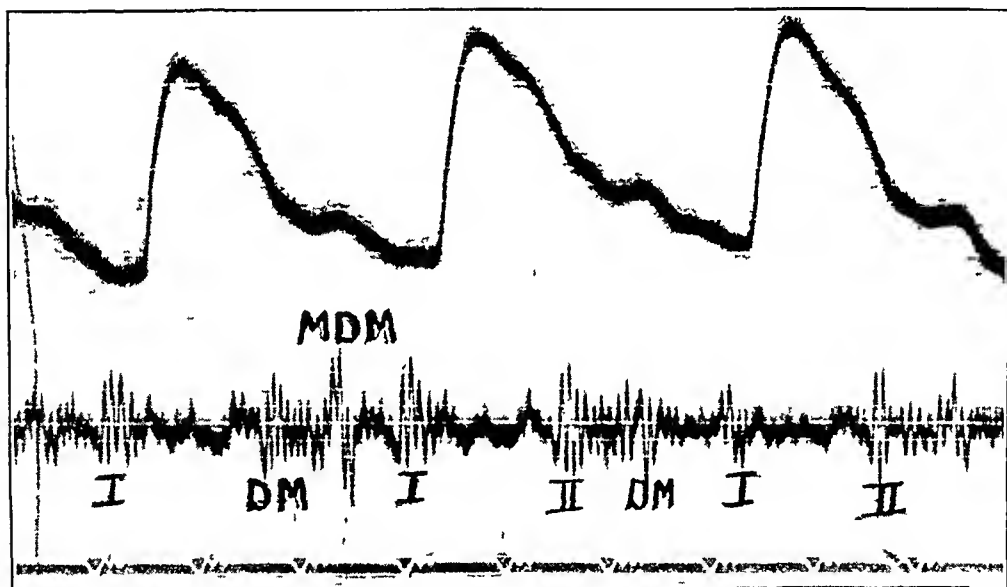


Fig 12—Radial pulse and phonocardiogram of case with mitral lesions, showing peculiar first and second sound vibrations and a pronounced diastolic murmur (DM) which sometimes increased in intensity during mid-diastole, as shown at MDM Details in text

with the phases of respiration The second sound is often indicated (II) but is followed immediately by a diastolic series of vibrations having a high frequency and of approximately the same period in successive vibrations, which is typical of musical murmurs It is loudest early in diastole and becomes diminuendo

CASE J-10—Mr Z Z Soft blowing systolic murmur at the apex, sixth intercostal space, 14 cm from the midsternal line Presystolic crescendo murmur in the left fourth intercostal space Soft systolic murmur and loud diastolic murmur over the left second intercostal space, transmitted across the sternum First sound of poor quality, pulse quite large, Corrigan type (Dr Meara)

Phonocardiograms recorded from the apex (Fig 12) show a series of miscellaneous vibrations from which the first sound could not be detected without the guidance of the radial pulse curve With its aid they were marked (I) They consisted of a few vibrations quite unlike those found in normal hearts and corroborate the auscultatory findings of a sound with poor quality No clear evidence of the soft systolic blow exists The second sound (II) in some cycles contains vibrations of larger amplitude than the first sound and is followed by a distinct, irregular series of vibrations (DM) responsible for the diastolic murmur In others, it is entirely replaced by the diastolic murmur It is curious how readily diastolic murmurs are registered

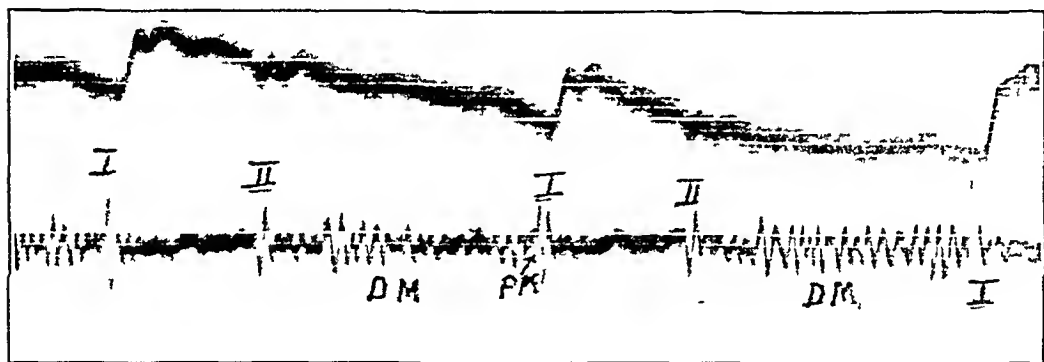


Fig 13—Radial pulse and phonocardiogram from a case with mitral lesions Phonocardiogram shows, in addition to first and second sound, presystolic (PM) and diastolic murmurs (DM), varying from cycle to cycle

from the apex in cases even when they are not audible in this locality but distinctly present over the more basal portions of the heart Frequently the diastolic murmur develops a series of larger vibrations in mid-diastole (MDM) which possibly corresponds to the murmur referred to as presystolic in the auscultation notes and heard somewhat higher on the left side Incidentally, attention may be directed to the fact that the descending limb of the radial pulse, which to the finger gives the sensation of a collapsing pulse, falls rather slowly The diastolic notch, however, is low and late in diastole

CASE J-12—Mrs A R *Mitral lesions* Apex beat sixth intercostal space, presystolic murmur ending in accentuated first sound at the apex Diastolic murmur over the second intercostal space and the sternum (Dr Sheldon, Cornell Medical Dispensary), also heard over the apex

Phonocardiograms taken from the apex are shown in Figure 13 The first sound (I) is indicated by a few large vibrations It is imme-

diately preceded by a series of small vibrations (PM) running into the larger vibrations of the first sound. These probably represent the presystolic murmur heard on auscultation. The systolic period is free from vibrations. The second sound (II) is composed of two large vibrations and is followed after a short interval by a series of coarse waves of relatively large amplitude and irregular periods (DM). They continue throughout diastole and sometimes merge into the presystolic vibrations or the first sound. They correspond to the diastolic murmur.

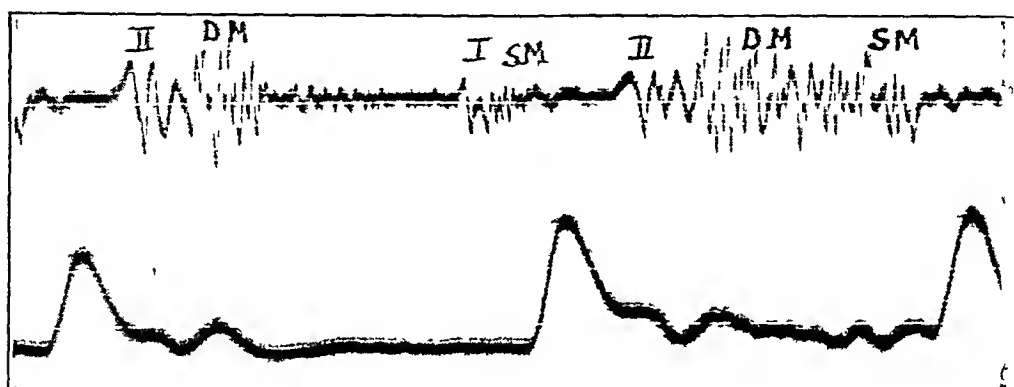


Fig 14—Phonocardiogram and radial pulse taken from a case with mitral lesions, showing, in addition to abnormal first and second sounds, a short systolic murmur (SM) and diastolic murmur (DM) varying from cycle to cycle both as to character and duration.

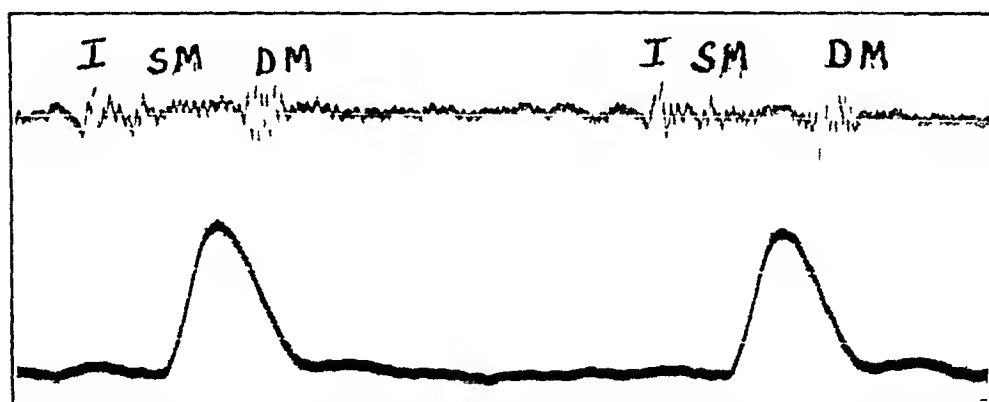


Fig 15—Phonocardiogram and radial pulse from a case of mitral regurgitation, showing systolic (SM) and diastolic (DM) murmurs, together with a collapsing pulse in the radial artery.

CASE J-13—Mr S C. *Probable mitral lesion.* At the apex are heard a soft systolic murmur and a diastolic rumble varying in duration, quality and intensity. At times a presystolic murmur accompanied by a thrill was present (Dr Niles).

The apex phonocardiogram (Fig 14) shows the first sound (I) either entirely supplanted by or continued into a murmur (SM) extending through the early part of systole. The second sound (II)

is followed after a short interval by a murmur (DM) composed of coarse, irregular vibrations. In some beats they extend throughout diastole, in others, occur only in the early part of diastole. No evidence of a presystolic murmur is present in any record. The descending limb of the radial pulse shows a rapid fall, corresponding to the collapsing character felt on palpation.

CASE J-15—Mr. O. E. *Aortic insufficiency*. Systolic murmur at the apex. Diastolic murmur over the aortic area and across the sternum. Collapsing pulse (Dr. Miller).

Phonocardiograms taken over the sternum (Fig. 15) show a first sound (I) of abnormal character followed by a series of systolic vibrations (SM) representing the murmur heard best over the apex in auscultation. These vibrations continue throughout systole. The second sound is replaced entirely by a series of vibrations (DM) which constitute the early diastolic murmur. The descending limb of the radial pulse falls rapidly, confirming the tactile impression of a collapsing pulse.

IV. SUMMARY OF TYPES OF CARDIAC MURMURS IN PHONOCARDIOGRAMS

Having analyzed the phonocardiograms individually, it remains in conclusion to group the various types of murmurs exemplified in a more orderly array and correlate them with the auscultatory phenomena.

Presystolic Murmurs—A presystolic murmur may accompany a variety of cardiac conditions. It is most clearly recognized in cases of mitral stenosis in which the auricle continues to contract regularly and efficiently. In such cases the murmurs increase in intensity and end in a characteristic snapping first sound from which alone the diagnosis may sometimes be made. The vibrations responsible for this murmur may be felt as a thrill on palpation and end in a characteristic systolic shock. Such murmurs are illustrated in Figures 8 and 10. When the auricles are fibrillating the presystolic murmur does not always disappear, but the presystolic period may be filled with vibrations continued from the diastolic murmur. This is shown in Figures 6 and 13. Presystolic murmurs may be present in double mitral lesions in which insufficiency predominates. In such cases the murmur does not necessarily end in the typical sharp first sound but is separated from it by a short interval, as shown in Figure 9. Finally presystolic murmurs frequently accompany aortic insufficiency. They may be separated from the diastolic murmur by an interval but not necessarily as shown in Figure 4.

Systolic Murmurs—Systolic murmurs of soft, blowing character most frequently accompany mitral insufficiency. They rarely replace the first sound entirely, although the character of this sound may be altered, as shown in Figures 6, 9 and 14. Systolic murmurs are also commonly associated with the diastolic murmurs in aortic insufficiency. Such cases are shown in Figures 4 and 15. Associated mitral or tricuspid lesions or aortic stenosis are, no doubt, sometimes responsible for this systolic murmur. It is possible, also, that the disturbed dynamic pressure relations between the ventricles and aorta in a pure insufficiency may in itself be sufficient to account for the systolic murmur.

Diastolic Murmurs—Diastolic murmurs may be described as early diastolic, middiastolic and late diastolic. The diastolic murmurs of aortic insufficiency usually occupy the early phase of diastole and may entirely replace the second sound (Fig 15). They may, however, in undoubted cases extend well into the diastolic period, as shown in Figures 3 and 4. Musical diastolic murmurs follow the second sound and are early diastolic in time, as shown in Figure 11. In no case was such a murmur found to extend into the late diastolic period.

Diastolic murmurs frequently occur in mitral lesions when the auricles are fibrillating. The murmur then varies from cycle to cycle and may fill the entire period of diastole, as shown in Figure 6. They may occur also in mitral stenosis while the auricle is regularly contracting but the rhythm of the heart is slow. This is exemplified in the records of Figure 13 where it is followed in certain beats, by a presystolic murmur. In complex mitral lesions systolic and diastolic murmurs may be so prolonged that they merge, thereby obliterating the intervening first sound as an entity (Fig 14).

THE PREVENTION OF SIMPLE GOITER IN MAN ~

SECOND PAPER

O P KIMBALL, M D, AND DAVID MARINE, M D
CLEVELAND

In Article I¹ we gave a brief review of the experimental work on which the assertion is based that simple goiter is probably the easiest of all known diseases to prevent. We gave a survey of the incidence and types of thyroid enlargement in the schoolgirls of Akron (Ohio) from the fifth to the twelfth grades, inclusive, and the plan of prevention used.

The plan in operation was arranged from the standpoint of simplicity, practicability, economy and the possible scientific value of the data obtained. First, a census of the condition of the thyroid gland was taken of all girls between the fifth and twelfth grades, inclusive, and the findings recorded on individual cards. This card will be used throughout the whole series of observations, the condition of the thyroid noted each year and a record of all treatment kept on the back of the card.

No		Date
Name		School
Age	Weight	Physical Development
Grade		Class Standing
Tonsils-Adenoids		
Thyroid		1
Simple		2
Adenomas		3
Thyroid tract		4
Duration		
Remarks		

It was planned that the thyroid examinations should be made by a single examiner in order to make the standard used constant, and the data obtained uniform. At the time of the first examination however, it was clearly foreseen that Dr. Marine would be called to military duty. Therefore, in order that the junior author should be trained to examine and classify the cases in the November examination as nearly as possible precisely in the same way as was done in the April examination, the April examination was made by both authors conjointly. It is obvious that much of the value of observations of this kind must depend on the uniformity of the methods and classification.

* Submitted for publication March 2, 1918

* From The H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University

1 The Prevention of Simple Goiter in Man, Jour. Lab. and Clin. Med., 1917, 3, 40

The thyroid glands were examined from the standpoint of Normals, Slight, Moderate and Marked Enlargements, Adenomas, Persistent Thyroglossal Tracts, and the girls for gross manifestations of myxedema, or exophthalmic goiter. No obvious case of either myxedema or exophthalmic goiter has been found.

Under *Normal* we have included all glands (a) which are not visible as a bulging of the skin across the trachea, (b) having a barely detectable band of thyroid tissue across the trachea on palpation, and (c) absence of a well defined thyroglossal stalk (so-called pyramidal process).

The cases with *Enlarged Thyroids* have been divided into three arbitrary groups (1) Slight, (2) Moderate and (3) Marked Enlargement. Under *Slight Enlargement* we have grouped those cases with (a) visible bulging of the skin over the thyroid isthmus (except in very stout children), and (b) a widened and thickened isthmial band or mass on palpation. If the isthmus can not be seen or felt, it can be felt by having the child swallow while the finger or thumb is held against the trachea just below the cricoid cartilage. Under *Moderate Enlargement* we have grouped those with gross deformity, bulging of the neck laterally from the enlarged lobes and marked bulging of the skin anteriorly from the enlarged isthmus. Under *Marked Enlargement* we have grouped those cases with excessive deformity.

Analysis of Thyroid Examinations—In April, 1917, 3,872 girls of the fifth to twelfth grades, inclusive, were examined and the general results are given in Table 1. In November, 4,415 girls of the fifth to twelfth grades, inclusive, were examined and the new records are given in Table 1. The new records each year will be classed in this table.

TABLE 1—CONDITION OF THYROID GLAND

	Normal		Slight Enlargements		Moderate Enlargements		Marked Enlargements		Adenomas	
	Pupils	%	Pupils	%	Pupils	%	Pupils	%	Pupils	%
April, 1917	1 688	43.59	1,931	49.88	246	6.35	7	0.18	29	1.01
Nov., 1917*	831	47.00	820	46.20	121†	6.80				

* Fifth grade girls and girls who entered the Akron schools since April, 1917.

† This number is greater than it would be if only fifth grade pupils were examined, two large schools, one a high school, accidentally destroyed all records of those girls not taking treatment, and therefore had to be recorded as new records.

For the prophylactic treatment we selected sodium iodid on the grounds of economy and ease of administration. Regarding the amounts that should be given, we had no data except from animal experimentation, and as we have pointed out repeatedly, exceedingly small amounts of iodin are effective. In all our dispensary work with children we have used either syrup of hydriodic acid or syrup of ferrous iodid, in 1 cc doses daily for two or three weeks, repeated twice yearly. The dosage is much less than the therapeutic dose of

iodids in other instances in which they are so extensively used, and there can be no reasonable doubt that the action is very different

We, therefore, arbitrarily selected to use 2 gm sodium iodid, given in 0.2 gm doses each school day, for each pupil in the fifth, sixth, seventh and eighth grades, and 4 gm in 0.4 gm doses each school day for each pupil in the ninth, tenth, eleventh and twelfth grades. These amounts were given in May, 1917, but in November, 1917, we gave 2 gm to each pupil from the fifth to twelfth grades, inclusive, since this amount in the year's use gave such definite results. As was pointed out in the previous paper, it was thought likely that the dose would be materially reduced. This amount (2 gm) will be given again in April, 1918. The treatment is given at the school by the teacher or principal and the number of doses recorded. A record is kept, both of those who take the treatment and of those who do not, and all pupils are to be examined annually and the thyroid conditions recorded.

A complete reexamination of all girls from the fifth to twelfth grades was made in November, 1917. There were 1,772 new records (Table 1). These include (a) this year's *fifth* grade, (b) pupils of all grades above the fifth entering Akron schools since April, 1917, and (c) all the girls in two schools (*not* taking treatment) whose records had been accidentally destroyed (see footnote, Table 1). All those previously examined were classed either as taking prophylactic treatment or not taking prophylactic treatment. The results are summarized in Table 2.

TABLE 2—SUMMARY

Pupils Taking Prophylactic Treatment	Pupils	%	Pupils Not Taking Prophylactic Treatment	
			Pupils	%
Thyroids remained normal	283	100.00	637	74.0
Increased from normal to slight goiter	0	0.0	259	26.0
Small goiters (unaltered)	287	66.0	759	87.0
Small goiters (disappeared)	141	33.5	10	1.2
Small goiters (increased)	2	0.5	103	11.8
Large goiters (unaltered)	34	66.7	106	95.5
Large goiters (decreased)	17	33.3	5	4.5
Total	764		1,879	
Total number of girls examined	4,415			

It will be seen that not a single pupil in whom the thyroid was normal last year and who took iodin, showed any enlargement, while of those not taking iodin, 26 per cent showed definitely enlarged thyroids—some moderately large goiters. Even more than a prophylactic action is shown in the results—just one third of the goiters marked “small goiters” disappeared, and one third of those marked “moderate goiters” showed a decrease of 2 cm or more. Accordingly, a distinct therapeutic effect is clearly demonstrated.

It was suggested by some physicians that we would have many cases of iodid rash. We spoke of this possibility in every school and asked the principal and teachers to look for symptoms and call the

attention of the school nurse and physician to every possible case. There were more than a thousand girls who took the full treatment, and only five developed any noticeable rash. None of these gave any trouble and the condition lasted only three or four days. Four of the girls continued the treatment and paid no attention to it, while the fifth asked to be excused from further treatment and the rash promptly cleared up.

As to the possibility of producing symptoms of Basedow's disease by giving iodine (in small doses) to a large number of girls indiscriminately, we can say that we have not seen a single instance in which any sign of such an effect was produced.

The earnestness with which the school girls have taken up the prophylaxis of goiter is encouraging for the practical application of this work. It is entirely elective on the part of the girls, and last year 1,080 girls finished the treatment. This year approximately 2,000 girls are taking the treatment.

SUMMARY

1 Simple goiter can be prevented by the administration of small amounts of iodine.

2 One third of the cases of uncomplicated simple goiter disappear or are markedly decreased by the use of a small amount of iodine, given internally.

3 There is no danger of producing a toxic condition ("Basedow's disease").

4 A very small proportion of the cases (at most 0.5 per cent) may develop an iodine rash, which promptly clears up on stopping the treatment.

We wish to thank Prof. H. V. Hotchkiss (Superintendent of the Public Schools), the Board of Education and the Principals of the several schools, through whose excellent organization and system, as well as the interest in the problem, the work was made possible.

THE CLINICAL SIGNIFICANCE OF THE ABNORMALLY WIDE VENTRICULAR DEVIATION IN THE ELECTROCARDIOGRAM *

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Electrocardiographic curves have given us exact and conclusive graphic records of many and varied types of cardiac arrhythmias. They have also offered some evidence as yet inconclusive regarding the presence of right and left ventricular hypertrophies. Furthermore electrocardiograms have been of aid in diagnosing main branch lesions of the auriculoventricular conduction system, in isolated instances the electrocardiographic diagnosis has been supported by pathologic examination of the heart. Because of the importance and clinical significance of myocardial disease attempts are constantly being made to interpret the condition of the myocardium from the electrocardiogram.

In an electrocardiographic study of a series of patients with valvular, and with myocardial disease¹ I have observed a characteristic which seems of importance in the diagnosis of myocarditis namely the abnormal width of the main deviation of the ventricular complex, commonly called the R-wave or the first ventricular spike. The width of the normal R-wave has been variously estimated. Hirshfelder² estimates it as 0.02 of a second. Lewis³ as from 0.03 to 0.04 of a second. Though not directly mentioned by Einthoven⁴ or Nicolai⁵ measurements of a number of their normal ventricular complexes give an average width of less than 0.05 second. All these measurements have reference to R-waves of normal form that is those that are neither split nor splintered and whose sides form rectilinear lines which meet

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1 The diagnosis myocarditis is often made on insufficient grounds for example, on the presence of soft murmurs and presumed enlargement of the cardiac area to percussion. By myocarditis I mean severe pathologic damage to the myocardium, more often evidenced by hypertension aortitis, precordial distress, decompensation and the probability of coronary disease rather than by auscultatory signs. The term cardiosclerosis I mean to apply to clinical conditions in which in addition to coronary and aortic disease there are assumed to be thickening and degenerative changes of the valves and endocardium in addition to myocarditis.

2 Hirshfelder Diseases of the Heart Ed 2 p 89

3 Lewis Heart 1912-1913 4, 242

4 Einthoven Pflüger's Arch f d ges Physiol 1912 63, 152

5 Nicolai, Handb d Allg Path u Krankh d Herz u Gefässe 3, Part 1

at a sharp angle and form a sharp apex. In the measurements of my cases I have included only clean-cut deviations of normal form. As an arbitrary standard in my series I have adopted a base line width of 0.07 or over as representing abnormally wide deviations. From my own measurements of many ventricular deviations of patients with normal hearts, and from the normal standards of others, I believe that 0.07 of a second (or over) probably represents a deviation which has taken an abnormally long time for its completion. Indeed, in only one instance (M. G., Case 13) have I found the R-wave of a normal heart wider than 0.07 of a second.

Recently, Robinson⁶ pointed out the clinical importance of abnormally wide and splintered ventricular complexes as evidence of marked functional changes in the heart. Oppenheimer and Rothschild⁷ have shown that some cases of myocardial disease involving especially the subendocardial myocardium, present an R-complex of low voltage, wide base and irregular sides. They believe this occurs because myocarditis in this location interferes with the rapidity and uniformity of the spread of the electrical impulse through the heart by involving the superficial end branches of the conduction system. These observers have confirmed the deductions drawn from the electrocardiograms by the pathologic study of a number of necropsies. Eppinger and Rothberger⁸ have induced experimental destruction of various parts of the cardiac musculature by freezing with ethyl chlorid, or by the injection of destructive substances. Electrocardiograms were taken before and after the injections. When, for example, a strong nitrate of silver solution was injected in the deeper layers of the left ventricle either at the base or apex, there was a marked change in the ventricular deviation. Within five minutes after the injection the descending limb became shorter so that it no longer touched the base line, this shortening became progressive so that in about twenty minutes the R and T deviations formed practically a monophasic curve. Injections of nitrate of silver in the superficial layers, or in the anterior or posterior papillary muscles were not followed by the foregoing changes in the electrocardiogram. Injections in the right ventricle were not regularly followed by electrocardiographic changes, the most typical consisted in a widening and prominence of the S and T deviations. I mention these experiments in some detail because they have an important bearing on the present clinical study. We must assume that we clinically meet with focal myocardial changes probably at times similar in loca-

6 Robinson, *THE ARCHIVES INT MED*, 1916, **18**, 830

7 Oppenheimer and Rothschild *Proc Soc for Exper Biol and Med*, 1916, **14**, 57

8 Eppinger and Rothberger, *Wien Klin Wchnschr* 1909, **22**, 1091

tion and destructiveness to the experimental lesions quoted, yet in only a single instance in a study of very many cases of marked cardio-sclerosis did I observe an electrocardiogram which resembled that derived from Eppinger and Rothberger's experimental injection in the deeper layers of the left ventricle. It therefore seems unwarranted to draw deductions of the state of the pathologic process in the human heart from the type of experimental damage already quoted. This discrepancy may rest on the fact that the rapid experimental destruction of the myocardium produces some special change on the electrocardiogram, or that in almost every instance, in the human heart, where there are marked localized changes, there is also damage in other portions of the myocardium, that is, the local damage is only part of general myocardial disease.

In a description of cases assuming defective conduction in one of the main branches of the auriculoventricular bundle, Carter⁹ describes as characteristics of these lesions, a Q-R-S time exceeding 0.10 second, increased amplitude of the R deflections, and T-waves, often exaggerated and usually in a direction opposite to that of the prominent initial deflection. The initial deflections themselves are very frequently atypical in form in at least one lead, bizarre forms are common. The assumption of branch bundle lesions in these cases has recently been questioned (Oppenheimer and Rothschild¹⁰).

In the cases that I report there has been no reason to assume an abnormal path for the impulse, for the electrocardiograms possess none of the characteristics of the aforementioned groups. Except for the abnormally wide base line, the electrocardiograms are of the usual normal types in form and size. Some of the deviations are tall. That amplitude in itself, however, need not necessarily imply an abnormally wide base is shown in Figure 12, in which R I is quite tall though of normal width.

A glance at the summary in the accompanying table of cases shows that, grouping them by their clinical characteristics, in all instances but two (Cases 3 and 5), there was grave disease of the myocardium, that is, myocarditis represented an important part of the clinical entity. The two exceptions were cases of rheumatic aortic disease, in both of which ventricular hypertrophy was extreme. That abnormal prolongation of the time of electrical impulse is not due to decompensation itself is evidenced by the fact, as noted in the clinical histories, that many of the electrocardiograms were taken when the patients were perfectly compensated. Ventricular dilatation per se as a cause for the abnormally wide R could be excluded. First, there was no evidence of

9 Carter, *THE ARCHIVES INT. MED.*, 1914, **13**, 805

10 Oppenheimer and Rothschild, *Jour. Am. Med. Assn.*, 1917, **69**, 429

any extreme dilatation, certainly not in the compensated cases. Secondly, in a study of a large series of cases of decompensated valvular lesions, in which cardiac dilatation was presumably a prominent feature, I found no abnormally wide R. Nor had I there found any correlation between hypertrophies—even extreme—and the width of the R deviation. Whether in the present study Cases 3 and 4 may be regarded as evidence of myocarditis in addition to hypertrophy, it is impossible to say.

TABLE 1—GIVING DATA OF AUTHOR'S CASES

Case No	Clinical Diagnosis	Rhythm	Width of R in Hundredths of a Second	Remarks
1	Myocarditis, coronary disease	Normal	RII =0.07 RIII=0.08	Arrhythmia and death
2	Lytic aortitis, myocarditis	Interpolated extrasystole	RI =0.12 RII =0.07 RIII=0.13	
3	Rheumatic aortitis	Auricular fibrillation	RII =0.07	Massive ventricular hypertrophy, death in one year
4	Cardionephritis	Normal	RI =0.08 RIII=0.08	Precordial pains
5	Rheumatic aortitis	Normal	RI =0.10 RII =0.09 RIII=0.08	Massive ventricular hypertrophy
6	Cardionephritis	Normal	RI =0.10 RIII=0.07	
7	Cardionephritis	Auricular fibrillation	RI =0.08	Died in uremia coma
8	Myocarditis, arteriosclerosis	Sinus arrhythmia	RI =0.08 RIII=0.08	
9	Aortic aneurism	Normal	RII =0.07	Moderate amount of myocarditis at necropsy
10	Cardiosclerosis	Auricular fibrillation	RII =0.08 RIII=0.09	
11	Cardiosclerosis	Normal	RI =0.12 RIII=0.08	Aneurismal dilatation of the aortic arch

It will be noted from the table that the electrocardiograms showed an abnormally wide R in one or two leads, rarely in all three. In view of the fact that the leads draw off the current from various cardiac areas—breadthwise in Lead I, diagonally in Lead II, and lengthwise in Lead III—one may possibly assume that the diseased myocardium lay more in one plane of the current than the other, thus interfering with the quick distribution and spread of the electrical current in that particular plane.

It remains to indicate this important fact that while the cases mentioned show abnormally wide ventricular deviations and are apparently

indicative of severe myocardial disease, I have observed cases clinically similar to the above with perfectly normal electrocardiograms. The reason for this is not at present apparent.

CONCLUSIONS

An arbitrary standard of 0.07 of a second was fixed as representing the lower limit of abnormally wide ventricular deviations which were otherwise normal in form and contour. Thus standardized, an abnormally wide R was found in a series of patients, all of whom, with two exceptions, showed evidence of marked myocarditis. These two were cases of rheumatic aortic disease, with extreme ventricular hypertrophy. The presence of the wide R seemed to indicate, though its absence did not exclude, myocarditis. It had no relation to the height of the R, the pulse rapidity, the cardiac rhythm or to the underlying disease producing the myocarditis. In some of the cases, severe

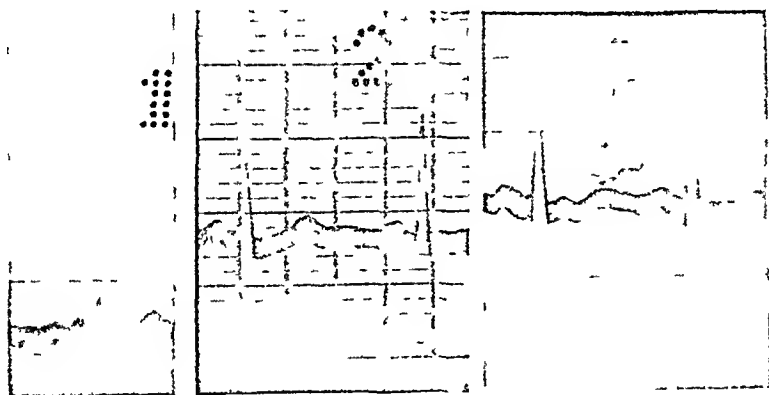


Fig 1—Electrocardiogram of A. G., Case 1. For description of this and tracings of following cases see the reports of cases from 1 to 11. In all the electrocardiograms the vertical lines measure 0.20 of a second.

decompensation was present, in others, it was absent. Though no definite statement of the fundamental cause of the abnormally long duration of the R phase can be offered, its frequent association with myocarditis would make it appear possible that this lesion acted as a direct hindrance to the proper normal, rapid propagation of the wave of electrical excitation through the ventricular musculature.

REPORT OF CASES

CASE 1—A. G., man, aged 54, had complained for two years of indefinite precordial pains radiating to the left hand, and of attacks of dizziness. He had been unable to work for several months because of these attacks. On examination, the systolic blood pressure was found to be 166, the diastolic 88. The first aortic sound was blurred, the second somewhat accentuated. The other heart sounds were normal. There was slight edema of the legs. The urine contained no albumin or casts. Fluoroscopic examination showed a normal sized aorta, the ventricular outline was somewhat enlarged to the left. The

electrocardiogram at that time (Fig 1) showed normal rhythm, R II and R III were respectively 0.07 second and 0.08 second in width. The subsequent history of the patient was of interest. Following the use of digitalis and of theobromin sodium salicylate, there was gradual improvement in the symptoms for about one year. The patient then developed sudden attacks of tachycardia, each of which lasted several days. The symptoms during these attacks were mainly subjective and consisted in the uncomfortable recognition of the rapid heart action, dyspnea was slight. About one week after the last attack he suddenly complained of precordial distress, followed by faintness. The patient was moderately dyspneic. Auricular fibrillation with rapid ventricular activity was present. A diagnosis of coronary thrombosis was made. Five days after

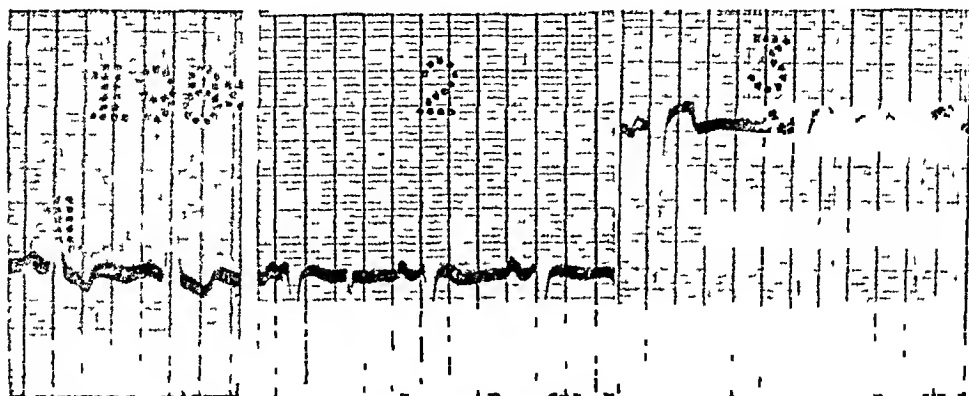


Fig 2—Tracing of W Z, Case 2

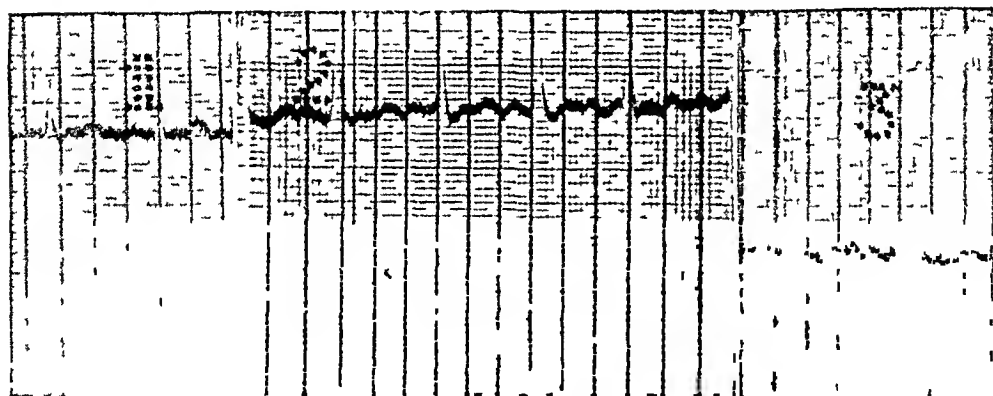


Fig 3—Tracing of H Y, Case 3

the onset of fibrillation, while sitting quietly on a chair and apparently quite comfortable, he suddenly gasped and died within a few minutes. The clinical diagnosis was myocarditis and coronary sclerosis.

CASE 2—W Z, man, aged 57, entered the hospital with general anasarca and the usual symptoms of cardiac decompensation. This had been the third break of compensation within recent years. The physical signs revealed the presence of an aortitis and of left ventricular hypertrophy. This was corroborated by roentgenography, which showed in addition, aneurismal dilatation of the entire thoracic aorta, and ventricular enlargement which practically filled the lower left half of the chest. The Wassermann blood examination was 4+. On antisyphilitic treatment, Karrell diet, digitalis and theobromin

sodium salicylate, the patient quickly improved. The electrocardiogram (Fig 2), taken when the patient was compensated, showed abnormally wide ventricular deviations in all leads, especially in the first and third, the R widths were respectively 0.12 and 0.13 second, R II was 0.07. The clinical diagnosis was syphilitic aortitis, myocarditis and left ventricular hypertrophy.

CASE 3—H Y, man, aged 31, had acute articular rheumatism six years prior to admission. Six weeks prior he suffered from what at first appeared to be grip, this was soon followed by fever and joint pains. He had never had any cardiac symptoms until recently. Examination revealed markedly throbbing carotid, subclavian, brachial and radial arteries. A rough systolic thrill was heard over the carotid and over the aorta in the jugulum. There was a

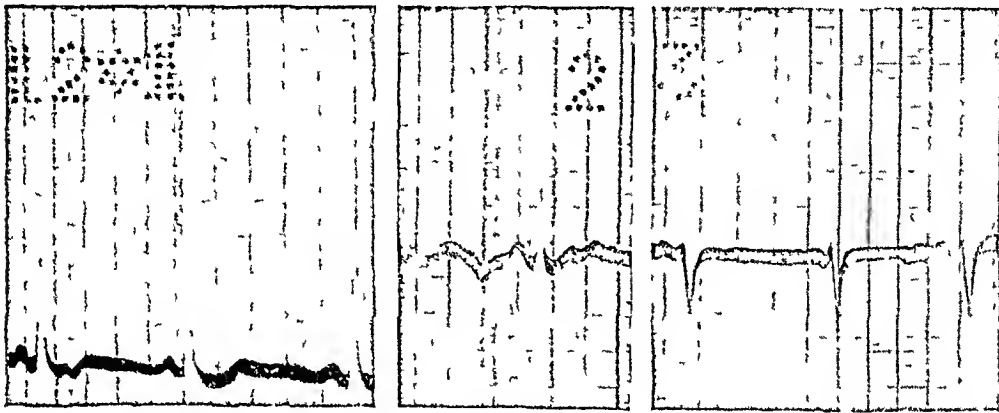


Fig 4—Tracing of I K, Case 4

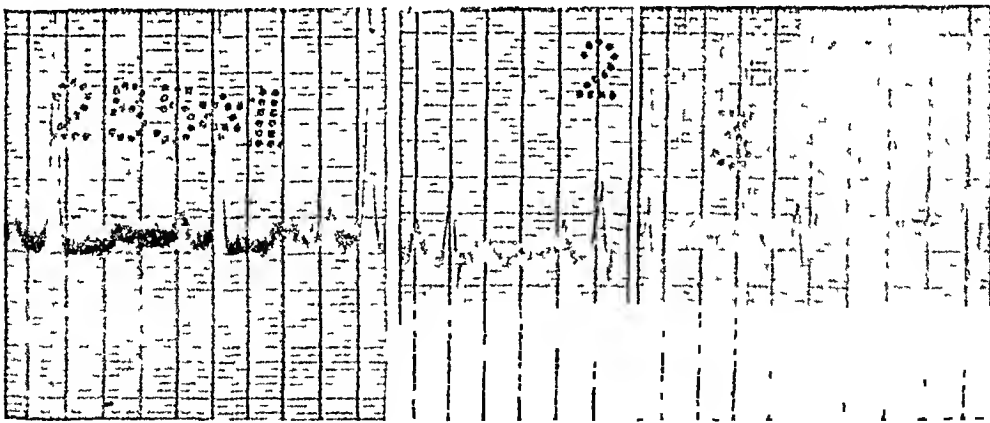


Fig 5—Tracing of E O, Case 5

loud, rough, double murmur over the right base. The liver was somewhat enlarged. The urine contained a trace of albumin and a few granular casts. The Wassermann blood examination was negative. The orthodiascope revealed an enlarged and hyperacting aorta, the left ventricle was moderately enlarged. The electrocardiogram (Fig 3) showed auricular fibrillation, the width of R II was 0.07. The patient developed hemorrhagic erythema of the legs, and later, rheumatic joint manifestations. He died within three months. The clinical diagnosis was a double aortic lesion and moderate left ventricular hypertrophy.

CASE 4—I K, woman, aged 57, complained for several years of a feeling of oppression in the chest and of numbness in the fingers of both hands.

There were also occasional attacks of nocturnal dyspnea accompanied by precordial pains. The systolic blood pressure ranged between 180 and 220, the diastolic between 90 and 110. There was a metallic second sound over the aorta, and a systolic murmur at the apex. With the fluoroscope, the aortic arch was found enlarged, the left ventricle moderately hypertrophied. The urine showed a trace of albumin and a few casts. R I and R III (Fig 4) were each 0.08 second in width. The clinical diagnosis was cardionephritis.

CASE 5—E O, woman, aged 21, had "growing pains" as a child. Her "heart trouble" began at the age of 10. The chief complaint was palpitation, especially after undue excitement. The systolic blood pressure was 180, the diastolic, 30 mm. The classical signs of a double aortic lesion and left ventricular hypertrophy were present. The orthodiascope revealed a violently pulsating aorta and massive ventricular hypertrophy, as well as enlargement of the cardiac shadow to the right. The electrocardiogram (Fig 5) showed the widths of the R deviations as follows: R I = 0.09 and R III = 0.08.

CASE 6—A K, man, physician, aged 53, had scarlet fever at the age of 15. Since then he had had occasional traces of albumin and casts in his urine. Of late, he had become somewhat dyspneic. The systolic blood pressure ranged between 175 and 190, the diastolic between 110 and 85. The second

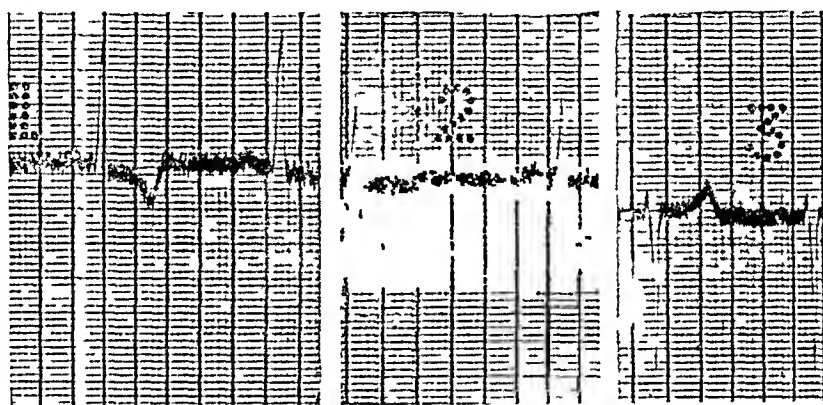


Fig 6—Tracing of A K, Case 6

aortic sound was somewhat accentuated, there was a systolic murmur at the apex. The liver was somewhat enlarged. The urine contained a trace of albumin, and granular and hyaline casts. There was slight edema of the legs. The blood Wassermann was negative. The orthodiascopic examination revealed a somewhat enlarged aorta and cardiac shadow. In the electrocardiogram (Fig 6), R I and R III were each 0.07 second wide. The clinical diagnosis was cardionephritis.

CASE 7—I W,¹¹ woman, aged 45, was brought to the hospital in a comatose condition. The only history obtainable referable to her present condition was that six years previously, when pregnant, she lost her eyesight (uremia?), labor was induced and her eyesight returned. At the present examination the heart was found hypertrophied, there was marked accentuation of the second sound at apex and base. The systolic blood pressure was 270 mm. A blood culture was sterile. The electrocardiogram (Fig 7) showed that R I was 0.08. Two days after admission the patient died in uremic coma. The clinical diagnosis was cardionephritis.

11 I am indebted to the electrocardiographic department of the Post-Graduate Hospital for the privilege of reporting Cases 7 to 10, with their corresponding electrocardiograms.

CASE 8—S M, man, aged 53 He complained for several years of dyspnea and precordial pangs, particularly on slight exertion He had had transient attacks of Cheyne-Stokes breathing, at such times his pulse was arrhythmic, electrocardiographic curves showed that the arrhythmia was of sinus origin The apex was in the sixth left interspace, 14 cm from the midsternal line The heart sounds were faint, there was a soft systolic murmur at the apex and a slightly accentuated second sound at the base The radial arteries were thickened and tortuous The systolic blood pressure was 190 mm, the diastolic,

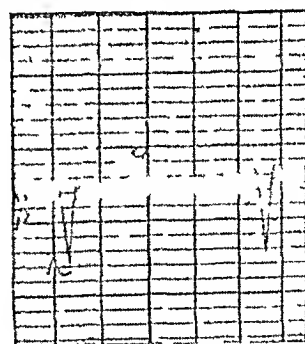
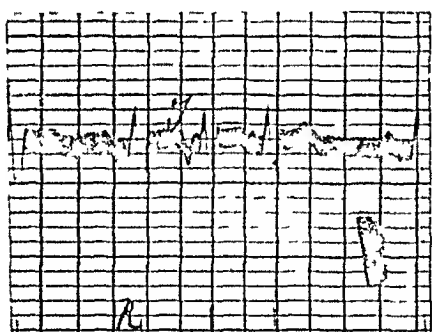
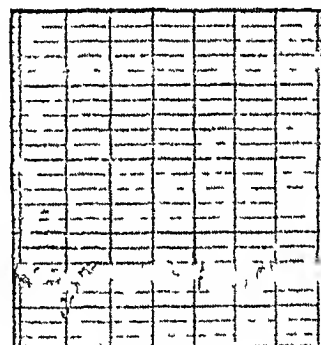
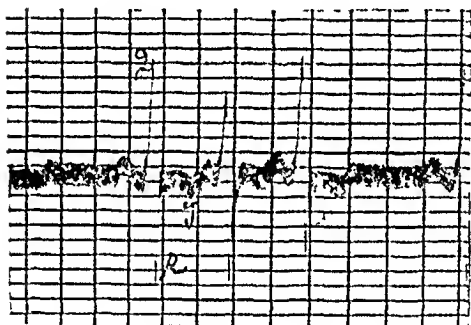
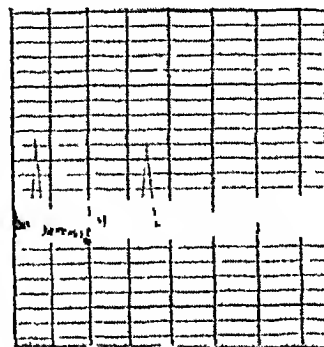
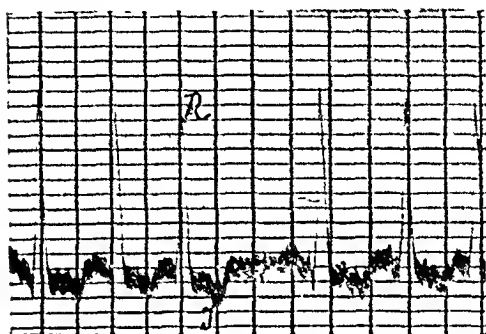


Fig 7

Fig 8

Fig 7—Tracing of I W, Case 7

Fig 8—Tracing of S M, Case 8

110 mm The electrocardiogram (Fig 8) showed that R I and R III were each 0.07 second wide The clinical diagnosis was myocarditis and cardio-sclerosis

CASE 9—J J, aged 53, man, had a very large, protuberant aneurysmal tumor the size of a large orange, situated at the upper right side of the chest There were loud systolic and diastolic thrills and pulsations over the aneurysm

there was also a systolic murmur and a systolic thrust at the cardiac apex. The apex was in the sixth interspace, 1 inch outside the nipple. Though the patient was somewhat dyspneic at first, there was no marked decompensation. R I and R III (Fig 9) were each 0.07. The aneurysm was wired. After some weeks, there were frequent external hemorrhages from the aneurysmal sac, the patient gradually succumbed. At necropsy, besides the aneurysm, the ventricles were moderately hypertrophied and showed a moderate amount of myocarditis.

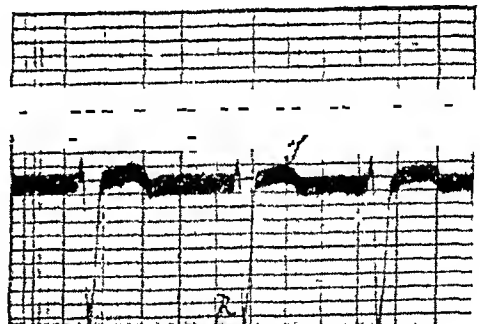
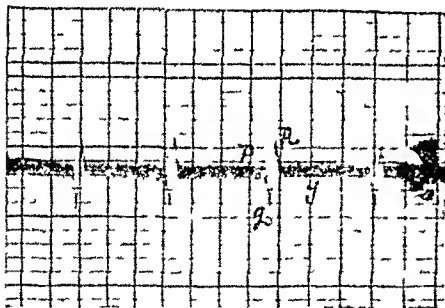
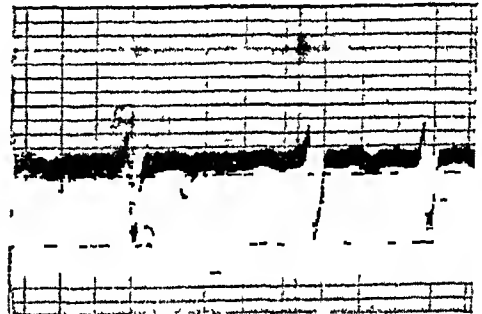
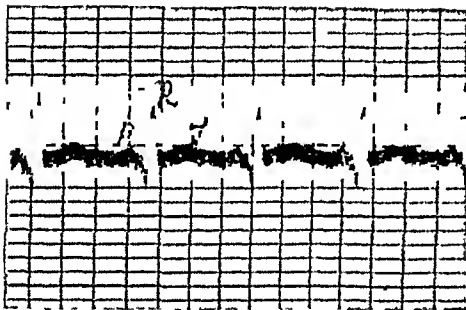
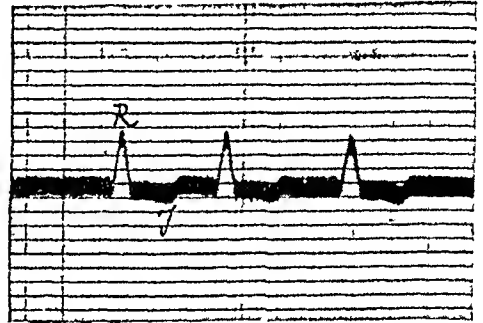
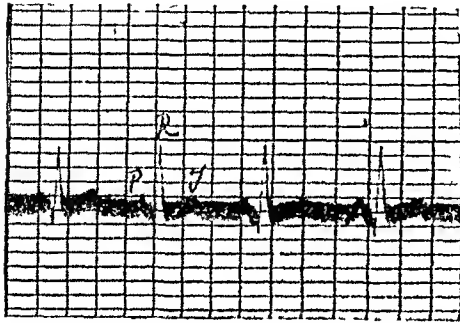


Fig 9

Fig 10

Fig 9—Tracing of J J, Case 9

Fig 10—Tracing of J C, Case 10

CASE 10—J C, man, aged 60, was addicted to alcohol. During the previous two years, he had had several mild attacks of dyspnea and of edema of the legs, the last attack occurred one week prior to admission. The cardiac apex was in the fifth interspace, 12 cm from the midsternal line. There was a blowing systolic murmur at the apex, the second sound at the base was impure and

slightly accentuated. The arteries were thickened. The electrocardiogram (Fig 10) showed auricular fibrillation, R II was 0.08 second, R III 0.09 second wide. The clinical diagnosis was cardiosclerosis.

CASE 11—M. M., aged 65, had rheumatism several years prior to admission. She had been somewhat dyspneic for several years, of late this symptom has become more marked. The first examination revealed mucous râles over the entire chest. There was a loud systolic murmur heard over the upper right chest, transmitted into the carotids and to the left of the scapula posteriorly.

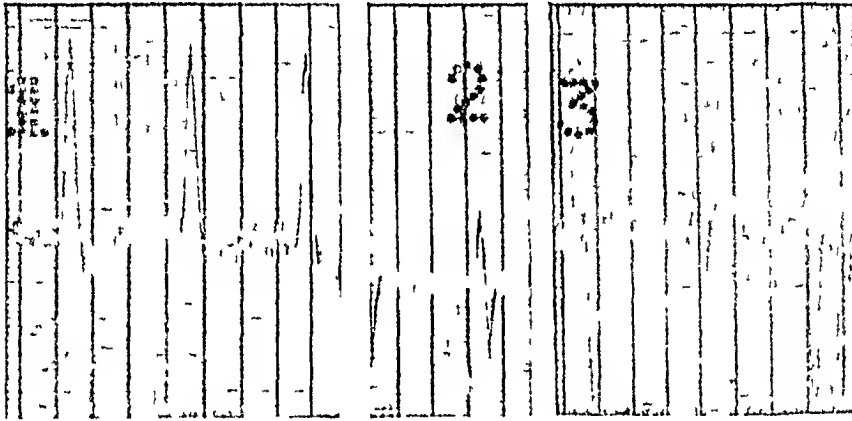


Fig 11—Tracing of M. M., Case 11

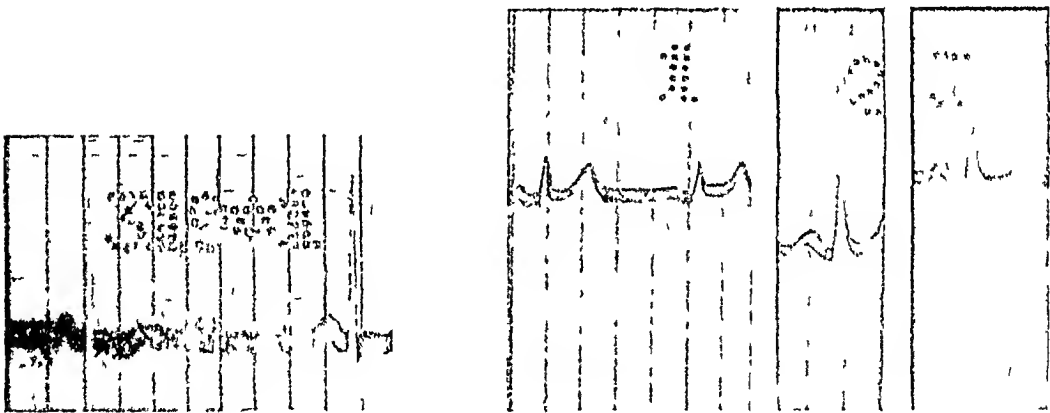


Fig 12

Fig 13

Fig 12—Electrocardiogram of a patient with cardiosclerosis, tall R of normal width (R = 0.04).

Fig 13—Electrocardiogram of a patient with a normal heart and wide R (R II = 0.08, R III = 0.08).

There was also a loud systolic murmur over the mitral area. The blood pressure was normal. There was slight edema of the legs. The urine showed a slight trace of albumin and a few casts. In the fluoroscope, there was found aneurysmal dilatation of the first portion and arch of the aorta, the heart was moderately enlarged. R I was 0.12 and R III 0.08 in width (Fig 11). The clinical diagnosis was cardiosclerosis.

THE VALUE OF TESTS OF KIDNEY FUNCTION

A DISCUSSION OF KIDNEY FUNCTIONAL TESTS WITH ESPECIAL
REFERENCE TO THEIR PROGNOSTIC VALUE ¹

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The use of the tests of kidney function has become so common a procedure in our hospitals in the past few years that little time need be wasted in recapitulating them. In general, four principles are involved:

1 The determination of the rate of excretion in the urine of a known amount of a chemical substance, injected or ingested

2 The determination of the degree of retention in the blood of various normal metabolic products

3 The comparison in a patient on a known test diet of the ingestion and excretion of nitrogen, sodium chlorid, water, etc

4 A determination of the ratio between the concentration of various metabolic products, ordinarily urea, in the blood, and their excretion in the urine, the result being expressed as a ratio of excretion or coefficient

Of the first group, the procedure most widely used is the phenol-sulphonaphthalein test of Rowntree and Geraghty, which determines the amount of the dye excreted in the urine during a two-hour period following the intramuscular injection of a definite amount. Indigo-carmin is also used, and in a recent communication Thomas and Birdsall¹ say that they consider it more trustworthy than phenolsulphonaphthalein.

Other tests are the lactose and potassium iodid tests used by Schlayer and Takayasu, as being analogous to the urea and sodium chlorid normally excreted. Theoretic objection to tests of this group may be made on the ground that the reaction of the kidney is tested to a foreign substance, and that normal metabolic products might and do show a different excretion rate.

In the second group, the concentration of the various nitrogenous constituents of blood has been particularly studied, and owing to the more recent methods of blood analysis introduced by Folin and Denis, Marshall, Van Slyke, Cullen, Benedict, and others, their determination has been rendered both easier and more accurate. Nonprotein nitrogen, urea nitrogen, uric acid, and creatinin have been the substances investigated, and much light has been thrown on the amounts normally present and their retention in pathologic conditions. Here, too, theo-

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* From St Luke's Hospital

¹ Thomas and Birdsall Jour Am Med Assn, 1917, 69, 1747

retical objection to the value of the tests may be made on the ground that they do not directly take into account the ingestion of fluid or protein, and that the concentration of the substance in question may be altered by either one of these factors, also, that the rate of excretion not being known, we do not know whether the concentration is being increased or diminished

The third method, a study of the excretion of substances normally eliminated, mainly of the water, nitrogenous bodies, and salt, and the comparison of these with the amounts present in the diet is a procedure elaborated by Hedinger and Schlager, and in the United States particularly studied by Mosenthal. This method, while having much to commend it, since the analytical procedures required are simple and there is a minimum of disturbance to the patient, is somewhat troublesome since it demands weighed diets and the accurate collection of numerous specimens of urine—not always an easy matter to secure in a general ward, as all of us who have had our struggles with careless orderlies realize only too well. The method further presupposes that the kidneys are the only factor in retention, which, as in the salt retention of pneumonia, we know is not always the case.

The fourth method, a comparison of the concentration of the salts, urea particularly, in the blood, with their excretion in the urine, the result being expressed as a formula, was suggested by Ambard, and the numerical result obtained is known as Ambard's coefficient. This coefficient expresses mathematically the ratio between the concentration of urea in the blood and its excretion in the urine, the normal numerical expression of which is 0.080, deficiency in function resulting in higher values.

At the time of Ambard's work in 1910, the determinations of urea in the blood were inaccurate and his formula was never widely used, but the present urease method of determining blood urea devised by Marshall and modified by Van Slyke, and the utilization of Ambard's law by McLean have resulted in the latter's so-called index of urea excretion, which gives the more readily remembered numerical expression of 100 as a normal, with lower readings due to deficient kidney function. Very high readings, however, are sometimes encountered in normal individuals and the meaning of these high variations is obscure. Fortunately the fluctuations in the lower pathologic readings are not so frequent though occasionally seen. This method has also the advantage of directly determining the blood urea, which forms one of the factors in the mathematical formula, and may be used for a check as a direct determination.

During the past three years there have been made in the chemical laboratory of St. Luke's Hospital numerous determinations covering the various forms of these tests. Of several thousand blood analyses

from many different types of cases, we wish to report only those made in definite cases of nephritis. Of these, the total number is 124, including over 1,500 separate tests, in most instances covering the complete series of analyses, that is, determination of McLean index, phenol-sulphonephthalein excretion, urea nitrogen, and nonprotein nitrogen. As our work confirms that of others in that abnormal findings are rarely encountered when the kidneys are unaffected, we have rejected those cases in which the disturbance was purely cardiac, with congested kidneys, and also such conditions as pernicious anemia, pneumonia complicating nephritis, etc., in order to narrow our problem to nephritis *per se*.

This reduces our list to 112 patients, on whom over 1,400 observations were made, covering more or less completely the entire series of tests. As abnormal in the above sense, we took a phenol-sulphonephthalein below 50, nonprotein nitrogen above 35, and urea nitrogen above 25 mg per 100 cc. For the upper limit of normal blood urea we adopted McLean's figure of 0.5 gm per liter, and 80 as a urea index, so as to eliminate those cases only slightly deficient in function.

The phenol-sulphonephthalein test was made according to the intramuscular technic of Geraghty and Rowntree. The nonprotein nitrogen, creatinin, and uric acid determinations were made according to the methods of Folin and Denis, with modifications introduced by Benedict and others. For the estimation of blood urea, Van Slyke and Cullen's modification of Marshall's urease method was employed. McLean's index of urea excretion was calculated according to his formula, the urine being collected over a seventy-two-minute period with the specimen of blood taken at the midperiod, thirty-six minutes.

By means of correspondence and the visiting nurse an effort was made to follow up the patients and find out about the present condition of all who had left the hospital alive. Of the 112 persons with nephritis, showing findings of abnormal kidney function, sixty-nine, or 61.6 per cent, died in the hospital or after leaving the institution. Twenty-four, or 21.4 per cent, were still living in varying conditions of health on the first of July, 1917, while nineteen patients, or 16.9 per cent, could not be traced. In general, the results given by all these tests are strikingly consistent, and the high percentage of fatal cases, 61 per cent, in a series of 112, is in accord with the indications furnished by the functional tests.

An effort was made to record graphically the course of renal function from the time of first observation to the time of death (Fig. 1). Our sixty-nine fatal cases are, of course, far too few to give a really accurate representation of such a curve, but as in many of them we have observations extending over a period of weeks or months, in one case over two years, the resulting curves, based on 685 separate determinations, are at least suggestive. The number of observations is, of

course, far in excess of the number of patients, and particularly in the case of phenolsulphonephthalein, blood urea, and the urea index, sufficiently large to be of value during the last three months of the patient's life

The figures on uric acid and creatinin, except during the last two weeks of life, are too few to be of much statistical value. At this period they are uniformly high. The average shown by the curves of phenolsulphonephthalein, nonprotein and urea nitrogen, and the urea index, seems to indicate a method which, if checked by a large number of

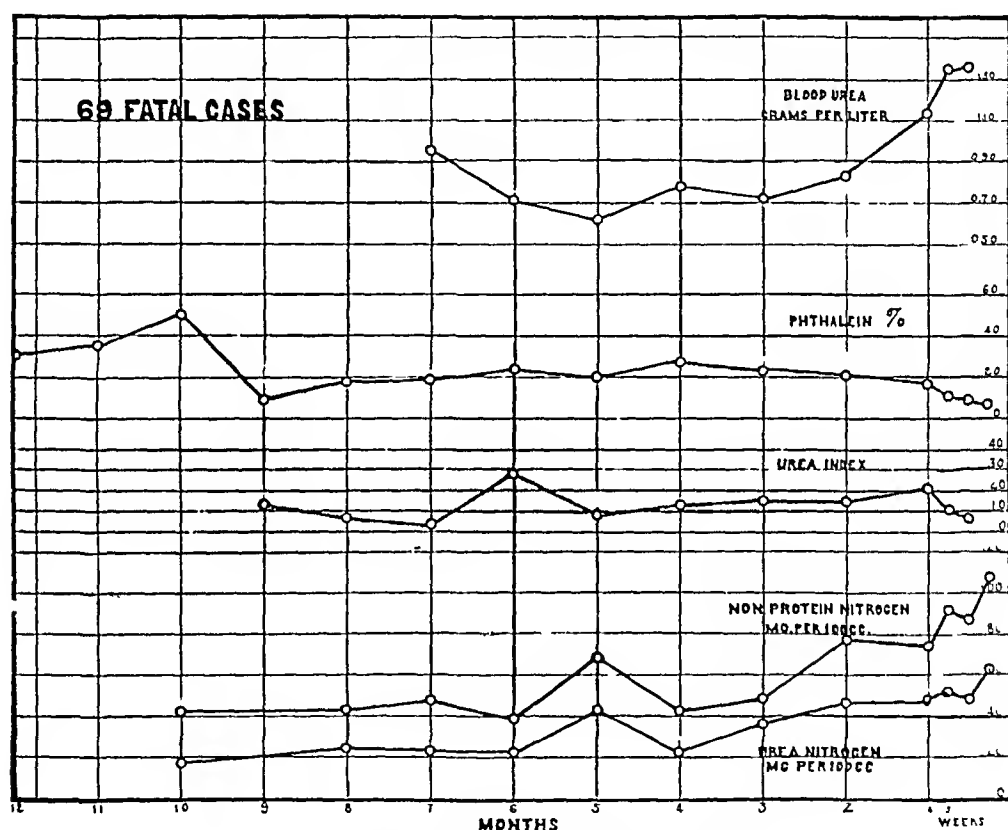


Fig 1—Curves based on 685 determinations

observations, might prove valuable in arriving at an average expectation of life for a given determination

The curves for the nonprotein nitrogen and urea nitrogen show a rapid rise during the three months preceding death, while during the earlier months there is a tendency for the curves to maintain a constant level. The elevation at the fifth month which disturbs the symmetry of the curves is caused by a single case in which the values were so high that the averages were disproportionately raised.

Many individual patients of course will have high retention values and still continue to live, as in the case of No 110,796 (Fig 3) who, five months after showing such figures as nonprotein nitrogen 160, urea index and phenolsulphonephthalein close to 0, was still living. Others

with normal values will die of uremia, for this high retention of normal substances is but the expression of abnormal function, and we must not blind ourselves to the fact that the actual poison in uremia is unknown, and that we have no test which expresses either its retention, or rate of excretion, yet, in the long run, the higher retention values and the lower excretion ratios indicate a kidney functionally so damaged as to be incompatible with life

A second chart, based on 450 determinations, has been prepared showing the averages of those cases still living July 1, 1917 (Fig 2) This of course has not the value of the first, and the curves show great

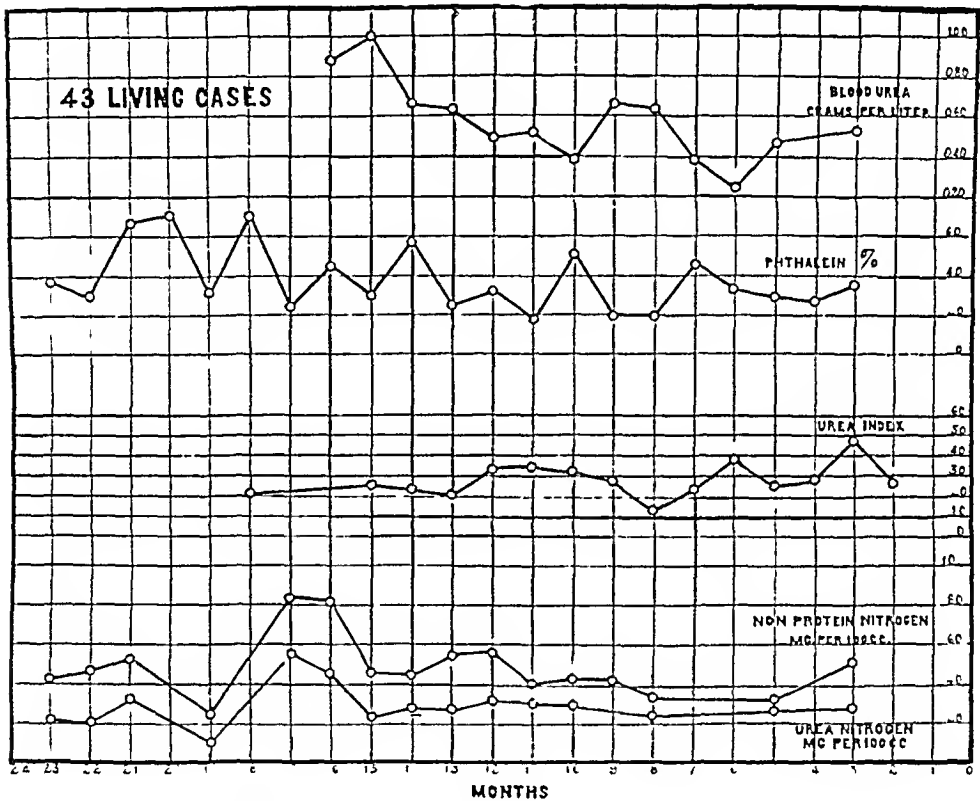


Fig 2—Curves based on 450 determinations

irregularity As an arbitrary date, July 1 was selected as the terminal point, and the series probably includes cases shortly to prove fatal, but the error tends toward the inclusion of abnormal rather than of normal values

One patient, 112,766 (Fig 4), the course of whose disease was followed for over three years, showed in her phenolsulphonaphthalein tests this impaired kidney function, her reading in 1913 being only 32 per cent She continued for many months with headache, slight hypertension, and urine of a specific gravity of 1.012 to 1.015, occasionally exhibiting slight exacerbations, showing the long period of time over which severe functional incapacity of the kidney may exist until death finally ensues

Jonas and Austin² have criticized the McLean index on the ground that the blood urea determinations are much easier in technic and equally valuable. In support of this contention, the authors cite their series in which only two cases appeared in which the index was abnormal and the blood urea normal. They state correctly that some difference of opinion exists as to what constitutes an abnormal blood urea, McLean's³ belief being that the normal range extends from 0.2 to 0.5 gm per liter, while Tileston and Comfort⁴ give 0.25 to 0.34 as normal limits. In our series 246 determinations show abnormally low indexes

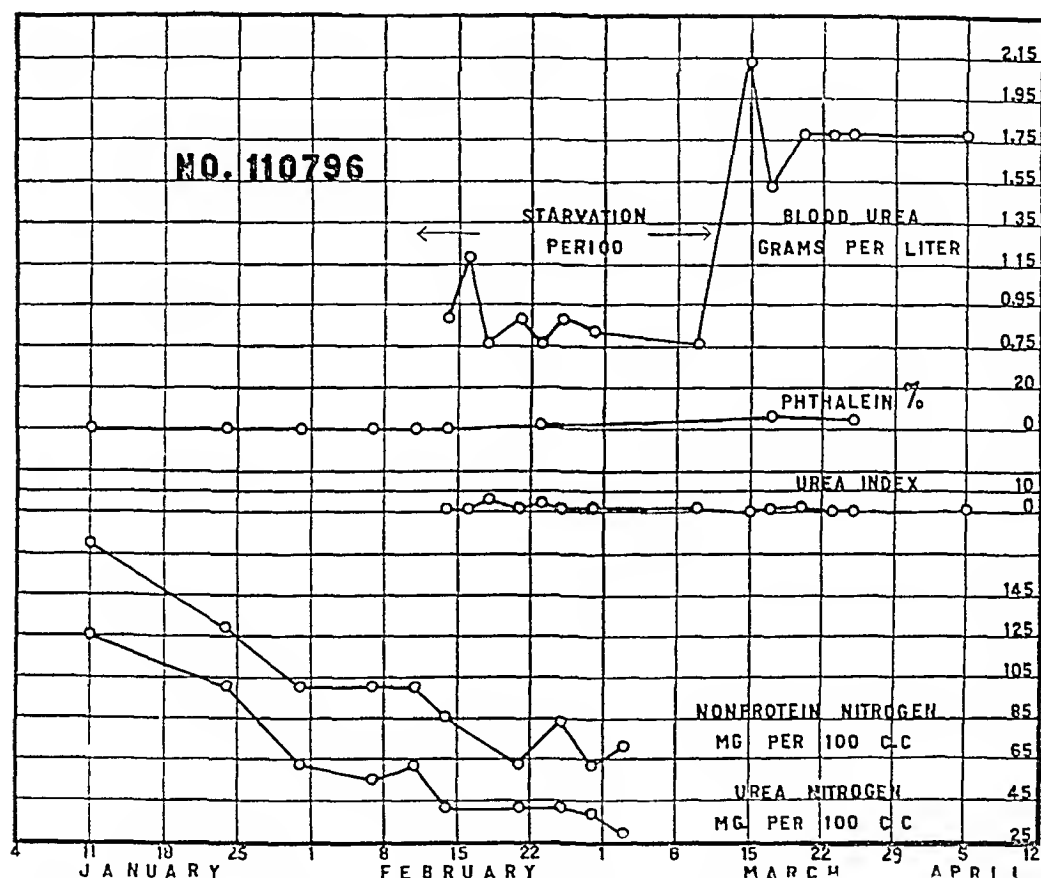


Fig 3—Note diminution in blood nitrogen retention during starvation period without alteration in phenolsulphonephthalein output or urea index. The record also illustrates the extreme retention values rarely seen over long periods.

Taking Tileston's normal as correct, thirty-nine, or just under 15 per cent, had normal blood urea values, while eighty-six, or 33.2 per cent, were within the normal range, if McLean's contention be correct. Our results therefore seem to prove that the delicacy of the index of urea excretion is much greater than that of a simple blood urea determina-

2 Jonas and Austin. *Am Jour Med Sc*, 1916, **152**, 560

3 McLean. *Jour Exper Med*, 1915, **22**, 212

4 Calculated from values of urea nitrogen given by these authors in *THE ARCHIVES INT MED*, 1914, **14**, 620

tion Fifteen to 33 per cent is far too great a discrepancy to disregard McLean⁵ has recently published two cases in which the state of urea excretion was studied at different levels of protein metabolism These observations confirmed those of Widal and Javal and showed that the state of the function of urea excretion remained unchanged even though great alterations in the concentration of urea in the blood took place

As a means of following the effect of diet, diuretics, etc, these methods have a very real value Take for instance the chart of No 110,796 (Fig 3), a sufferer from chronic interstitial nephritis with

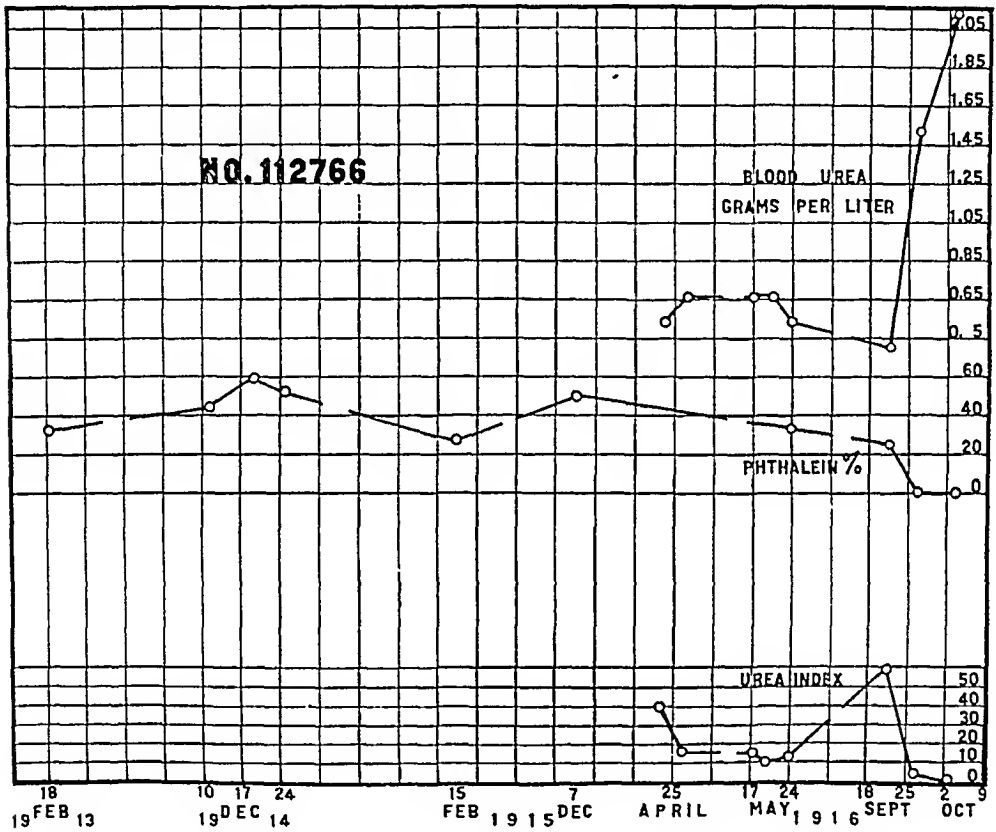


Fig 4—Showing the average type of case of moderate impairment of kidney function of several years' duration, with sudden rise in retention values and fall in phenolsulphonephthalein output during the last weeks of life

convulsions This patient was kept from February 11 to March 11 on a diet extremely low in nitrogen, at times containing almost no protein, and never above 30 gm The amount of blood urea on this diet fluctuates between 0.7 and 1.1 gm per liter, while on the resumption of a diet containing approximately 50 to 75 gm of protein the figures are raised to 1.55 to 2.1 gm per liter Neither the urea index nor the phenolsulphonephthalein, however, rose during this starvation period, and the

5 McLean Jour Am Med Assn, 1917, 69, 437

patient's condition, in spite of her improved blood urea retention, and her extreme nitrogen starvation, did not change materially. She left the hospital against advice and six weeks later was found by the visiting nurse in about the same condition, but it has been impossible to ascertain the subsequent course of her case. The results of the tests in this instance also illustrate the value of the index as compared with the simple determination of the blood retention products.

On the other hand, the improvement of Patient 111,478 (Fig. 5) with a chronic diffuse nephritis, abundant albumin and casts, and with a ++++ Wassermann accompanying a possible syphilitic nephritis is shown following the administration of a single dose of arsenobenzol after a preliminary period during which his tests, particularly his

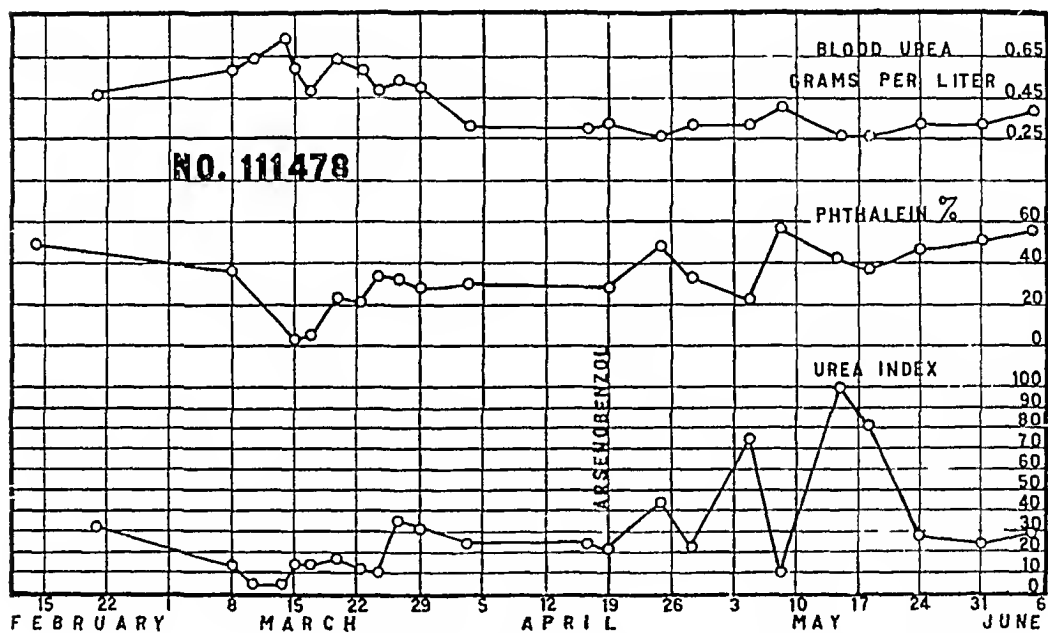


Fig. 5—Chart of a fatal case showing temporary improvement after administration of the arsenobenzol brand of arspenamin.

salt balance, were much impaired. The improvement was gradual, lasting until his discharge from the hospital, but it was subsequently learned that he died two months later.

In conclusion, it may be said

- 1 The kidney functional tests have a real prognostic value, particularly if the results are constantly abnormal on repeated examination.
- 2 The higher values for the blood retention products are found mainly in the terminal stage.
- 3 By plotting the curve of a very long series of cases it should be possible to arrive at an average expectation of life as indicated by any individual determination.
- 4 The value of diet and drugs may in the future be shown more clearly by these methods than by any others now available.

TABLE 1—FINDINGS IN SIXTY-NINE FATAL CASES

Case No	Age	Sex	Date of Examination	Phenol sulphthaldin, per Cent	Blood Analysis				Urea Index	Urine, Specific Gravity	Blood Pressure		Date of Death	Fundus	Diagnosis
					Mg per 100 Cc						Gm per L Blood Urea				
					Nonprotein N	Urea N	Uric Acid	Creatinin							
105912	15	♂	3/27/15 4/28/15 6/11/15 7/ 6/15	41.0 40.5 28.8 28.0		22.2 32.5 16.2	2.5			1.010-15	275	160	8/ 9/15		C I N, uremia
106720	59	♂	6/ 8/15 6/12/15	31.7	53.0	26.5				1.015-20	160	120	9/18/15	Negative	C I N, enditis
106820	53	♀	6/26/15 7/ 1/15 8/ 4/15	58.0 43.0 61.0	31.0 66.0	31.0				1.010-20	200	110	9/ 7/15	Negative	C I N
106861	16	♂	6/15/15 6/29/15	27.5	54.0	24.7	6.7			1.010	230	125	1/ 1/16		C I N, gout
107258	45	♂	7/ 5/15	Trace	50.0	33.0				1.010	250	210	7/11/15	Negative	C I N, uremia
107485	53	♀	7/17/15	25.0	13.0	22.0				1.010-20	300	210	9/30/15		C I N
107910	36	♂	8/ 9/15	17.0	50.0	27.0				1.005-20	205	150	8/16/15	Retinitis	C I N
108213	43	♂	8/27/15 9/ 5/15	5.0 Trace	125.0 250.0	63.0 115.0	4.1 11.0			1.015	210	140	9/ 7/15		C I N, uremia
108353	42	♀	9/ 6/15 9/15/15	41.7 3.3	45.0 66.0	25.0 36.0	6.2			1.020-25	120	90	9/17/15	Negative	C I N
108156	14	♀	8/ 2/15 9/13/15 9/22/15 9/27/15 10/ 4/15 10/11/15	14.5 Trace Trace Trace Trace Trace	63.0 111.0 73.0 166.0 117.0 100.0	31.0 83.0 50.0 62.5 71.0 22.0	7.1 7.6 8.3 7.1 10.9			1.010-20	200	155	10/18/15		C I N
108527	53	♀	9/13/15 9/17/15 9/22/15	9.6 11.0	91.0 77.0 113.0	71.0 60.0 62.5	3.8 6.2 8.3			1.010	200	120	9/23/15	Negative	C I N, uremia
108710	56	♀	9/22/15	18.2	59.5	35.5	7.1			1.015-20			9/28/15		C I N, uremia
108816	40	♀	9/27/15	Trace	125.0	82.5				1.010-20	275	185	10/ 5/15	Retinitis	C I N
109632	43	♂	5/28/15 8/25/15 11/17/15	5.16 62.5 22.0	53.0 45.0 25.0	21.7 22.0 15.0				1.020-25	135	125	12/ 3/15	Negative	C I N
109796	50	♂	11/16/15	Trace	112.0	82.0				1.020	260	160	11/20/15	Negative	C I N

Case No.	Sex	Date	Weight (kg)	Length (cm)	Temp (°C)	Heart Rate (b/min)	Respiratory Rate (r/min)	Blood Pressure (mmHg)	ECG	Urea Nitrogen (mg/dl)	Creatinine (mg/dl)	Other	
1110435	♀	12/22/15	200.0	125.0	11.2					1.010	0.25	Negative	
1110501	♂	12/29/15 1/4/16 1/8/16	49.5	31.7	0.5					1.010	0.25	7/5/16	
1110566	♂	12/23/15	51.5	31.7						1.005		2/26/17	
1110588	♀	1/12/16 1/24/16 1/31/16	71.5 67.0 143.0	50.0 50.0 100.0						1.005	15	2/7/16 Hemorrhage	
1111112	♂	1/23/16 2/4/16 2/9/16 2/11/16 2/14/16 2/16/16 2/18/16 2/21/16	100.0 100.0 83.5 83.5	71.5 62.5 54.2 50.0	3.5					1.010	15	3/3/16 Retinitis	
111477	♀	2/14/16 2/16/16 2/23/16 3/10/16 5/3/16 8/7/16 9/25/16 9/18/16	38.0 30.0 41.7 100.0 100.0	20.8 27.5 62.5 55.5	3.1 3.8					1.005	20	10/16/16 Retinitis	
111478	♂	2/14/16 2/21/16 3/8/16 3/10/16 3/13/16 3/15/16 3/17/16 3/20/16 3/23/16 3/25/16 3/27/16 3/29/16 4/3/16 4/16/16 4/19/16 4/24/16 4/28/16 5/5/16 5/8/16 5/15/16 5/19/16 5/24/16 5/31/16 6/7/16	37.0 49.0 36.2 4.5 5.6 23.0 21.7 33.3 32.0 28.6 30.0 30.5 28.5 48.2 33.8 22.2 56.7 41.7 37.5 46.2 51.0 55.6	25.0							1.005	20	8/12/16

TABLE 1—FINDINGS IN SIXTY-NINE FATAL CASES—(Continued)

Case No	Age	Sex	Date of Examination	Phenol sulphophthalcin, per Cent	Blood Analysis					Urea Index	Urine, Specific Gravity	Blood Pressure		Date of Death	Fundus	Diagnosis
					Mg per 100 Cc				Gm per L Blood Urea							
					Nonprotein N	Urea N	Uric Acid	Creatinin								
111480	44	♀	2/14/16		143 0	83 0					1 005 20	132	70	2/19/16		O I N, carditis
111567	48	♀	2/23/16 4/14/16 4/21/16	50 0	35 7				0 321 0 315	47 0 68 0	1 015 25	210	90	5/14/16	Negative	O I N, uremia
111590	16	♂	9/15/15 2/23/16 3/ 8/16 3/13/16	31 3 Trace Trace	33 0 56 5 122 6	11 0 35 7 62 5	3 1 3 0		1 780	1 6	1 010 20	120	75	4/ 9/16	Negative	O I N
112179	71	♂	4/16/16		100 0	50 0								4/16/16		O I N
112523	78	♂	4/16/16	43 3	28 5	15 0	5 0		0 383	27 5		165	100	10/ 5/16		O I N
112756	33	♂	4/26/16 5/ 1/16	40 0 30 8					0 530 0 535	8 0 30 0		200	165	1/23/17		Psychitis
112766	17	♀	2/18/13 12/11/14 12/21/14 12/25/14 2/15/15 12/ 7/15 4/26/16 5/17/16 5/19/16 5/24/16 9/ 4/16 9/21/16 9/27/16 10/ 4/16 10/14/16 10/27/16	32 0 44 5 59 4 52 4 27 9 50 3					0 535 0 667 0 668 0 667 0 535	40 0 16 0 15 0 10 0 13 0	1 001 20	242	164	10/28/16		C D N
				35 0	111 1	55 5			0 405 1 526 2 140	54 1 4 25 0 8						
112895	35	♀	1/28/16 5/ 8/16 5/19/16 6/ 5/16	51 4 43 3 23 6 9 0	167 0	83 3	6 09	2 9	0 667 0 667 0 667 1 070	24 5 23 0 12 0 7 0	1 010 15	230	150	6/19/16	Hemorrhages	O I N, uremia
112928	63	♂	5/ 1/16		30 0	14 0	4 54	1 0			1 010 25	150	120	5/10/16		O I N, uremia
113021	48	♀	5/ 3/16 5/ 5/16 5/15/16 5/22/16	10 0 7 1	92 0	50 0			1 070 0 934 1 187	6 0 46 0 2 8	1 010-20	260	160	6/ 3/16		O I N, uremia

TABLE 1—FINDINGS IN SIXTY-NINE FATAL CASES—(Continued)

Case No	Age	Sex	Date of Examination	Phenol sulph phthal ein, per Cent	Blood Analysis							Urea Index	Urine, Specific Gravity	Blood Pressure		Fundus	Diagnosis
					Mg per 100 C c			Nonprotein N	Gm per L Blood Urea								
					Urea N	Uric Acid	Creatinin		Gm per L Blood Urea								
1115989	29	♂	10/16/16 11/20/16	0 0					1 070 1 780	3 3 0 95		1 005 20	220	150		C D N, uremia	
1116117	75	♂	10/23/16 11/ 1/16	36 4	62 5	33 3	5 5	1 0	0 892	24 0		1 005 20	235	135		C I N	
1116673	47	♀	11/20/16	45 5					0 973	6 5		1 005 30	175	75		C I N	
11170 6	41	♀	12/ 7/16	40 0	31 3	16 1	5 0	0 8				1 005 20	124	94		C I N	
1117248	58	♂	12/21/16	33 7					0 630	17 4		1 015 25	210	70		C I N, earditis	
1117317	47	♀	8/11/16 8/28/16	21 4 12 5	38 5	25 0	8 9		0 446	12 5		1 010 25	210	110		C I N	
1117437	24	♀	1/ 3/17 1/22/17 2/12/17 2/23/17 3/ 9/17	67 40 0	125 0 125 0	83 3 83 5	5 6	2 5	0 713 0 714 1 100	8 5 7 0 2 0		1 005 20	220	160	Retinitis	C P N	
1117441	20	♂	1/26/16 2/ 7/16 2/25/16 2/28/16 3/ 1/16 3/ 3/16 3/ 6/16 3/ 8/16 3/10/16 3/13/16 3/15/16 3/17/16 12/ 6/16 1/ 1/17	53 0 37 2 49 0 38 8 46 8 43 0	50 0 62 2 50 0 50 0	27 8 38 5 31 2 25 0			0 667 0 535 0 507 0 667 0 761 0 759 0 667 0 761 0 763 0 667	22 5 23 5 26 3 21 6 18 1 18 4 21 2 21 5 21 5 17 4		1 010	175	100		C I N	
1117448	35	♀	1/ 1/17 1/10/17 1/17/17 1/31/17 2/ 9/17 2/28/17 3/ 7/17 3/30/17 4/20/17 6/ 8/17 7/ 2/17 7/ 6/17	25 0 10 0 15 6 7 0 15 0 20 0 13 0 15 7 8 0 21 4	111 0	66 8			1 338 0 715 0 890 0 972 1 070 0 821 0 616 0 790 0 890 1 130 1 340 1 785	8 1 5 5 6 0 9 0 5 0 32 0 7 5 8 0 8 0 5 0 2 4 1 5		1 008 20	220	110	Albuminuric retinitis	C D N	

TABLE 2—FINDINGS IN FORTY-THREE LIVING CASES

[illegible]

TABLE 2—FINDINGS IN FORTY-THREE LIVING CASES—(Continued)

Case No	Age	Sex	Date of Examination	Phenol sulphone phthalen, per Cent	Blood Analysis				Urea Index	Urine, Specific Gravity	Blood Pressure		Fundus	Diagnosis	
					Mg per 100 Cc						Gm per L Blood Urea				
					Nonprotein N	Urea N	Uric Acid	Creatinin							
115061	13	♀	10/ 1/15 10/ 6/15 10/27/15 12/ 1/15 8/23/16	50 0 50 0 55 6 66 7 63 6	36 5 20 0 21 0 18 0 25 0	16 0 11 0 7 2 11 7	5 08 1 65 1 25		0 315	39 5	1 005 30	120	80		A P N
115106	19	♂	8/25/16 1/ 3/17 5/ 7/17	66 7					0 382 0 112 0 268	15 0 85 0 79 0					C I N
115770	16	♀	6/23/16 9/22/16	25 0 10 0					0 111 0 960	27 0 1 22	1 005 20	238	170	Retinitis	C I N
115657	57	♀	10/ 2/16 1/31/17 3/ 7/17	11 1 28 7	71 5	38 5			0 713 0 668	12 5 17 0		230	120	Negative	C I N
115875	69	♂	7/ 3/16 10/14/16	12 8 31 5					0 535 0 535	11 0 25 0	1 005 25	170	90		C D N
115945	52	♀	10/14/16	70 0					0 821	10 7	1 020 25	210	110	Hemorrhages	C I N
116306	8	♂	10/ 5/15 10/20/15 10/30/15 11/ 5/15 11/23/15 12/ 7/15 12/23/15 2/ 9/16 3/11/16	63 0 80 0 10 0 71 1 74 3 23 6 86 7 83 3	50 0		3 2				1 010 30				C I N
117170	57	♂	12/27/16	71 4	38 5	21 7	2 75		0 255	19 4	1 010 25	230	220		C I N
117230	11	♀	12/21/16 12/29/16	31 6 71 4					0 199	71 0		210	180	Old hemorrhage	C I N
117501	69	♂	1/17/17 1/31/17 2/ 7/17	62 5 21 0 28 0					0 115 0 311 0 368	37 0 21 0 21 0	1 005 20	175	120		C N
117628	19	♂	12/ 9/16 1/25/17	29 0 25 0					0 128 0 185	21 0 27 0	1 010 15	200	110		C I N
118397	30	♀	2/21/17 2/28/17 3/17/17 3/14/17	27 3 51 2 70 0 50 0					0 255 0 128 0 382 0 267	20 0 33 0 31 0 153 0	1 010 25	130	85	Negative	C I N

STUDIES ON RENAL FUNCTION DURING AND IMMEDIATELY FOLLOWING SOME OF THE ACUTE INFECTIOUS DISEASES¹

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BOSTON

It is well known that definite anatomic lesions may occur in the kidney during the course of almost any of the acute infectious diseases. These lesions are usually, if not always, associated with clinical signs such as edema, scanty urine, the appearance of albumin in the urine, or abnormal findings in the sediment. The renal function as studied by various special tests is much impaired in these cases, as has been shown by Schwartz and McGill¹. Naturally such acute lesions in the kidney often result in permanent anatomic injury to the kidney, with or without disturbance in renal function.

In other cases during acute infections it is not uncommon to find albumin and casts in the urine without any other clinical evidence of renal disturbance. Also, during the course of an acute infection, there may be a decrease of substances normally found in the urine, such as the low chlorid content of the urine in pneumonia. It is not always clear whether these variations are due to renal disturbances or not. Still other cases during the course of acute infections fail to show any evidence of renal disturbance by the usual routine examination of the urine. The question arises whether or not these cases without apparent renal involvement would show any disturbance in renal function by the special tests more recently devised for the purpose, either during the febrile period or soon after. This is of especial interest in view of the tendency at present to force feedings during the course of many of the acute infections, which presumably puts an increased load on the kidneys.

Amid the variety of tests for renal function which have received considerable attention of late years, three or four stand out as being the most satisfactory for ordinary clinical work. In this clinic at present the renal function is studied by Rowntree and Geraghty's² test for

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¹ From the Department of Medicine, Harvard University, and the Medical Clinic, Peter Bent Brigham Hospital

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1 Schwartz, H, and McGill, C. THE ARCHIVES INT MED, 1916, **17**, 42

2 Rowntree, L. G., and Geraghty, J. T. Jour Pharmacol and Exper Therap, 1909, **1**, 579

the elimination of phenolsulphonephthalein in the urine after intramuscular injection, the estimation of the blood urea by the urease method of Van Slyke and Cullen,³ and the estimation of the index of urea excretion as determined by McLean's⁴ formula based on Ambard's laws. In addition, the renal function is investigated by studying the output and concentration of the urine and also of the sodium chlorid and nitrogen in the urine, collected at two-hour intervals during a day in which the patient is on Christian's⁵ modification of the renal test diet devised by Hedinger⁶ and Schlayer.

Although the last mentioned test is probably more comprehensive than the others, it is not so well adapted for acute infections, in which the patients often can not eat the required diet and find difficulty in voiding urine every two hours. Studies on renal function by means of some one or more of these tests during the course of acute infections have been reported by a few observers. Thus Tileston and Comfort,⁷ in 1914, reported on the urea in the blood in various acute processes. They found the nonprotein nitrogen and urea of the blood elevated, in cases of pneumonia during the fever, but not elevated in typhoid fever, acute rheumatism and uncomplicated scarlatina. Schwartz and McGill,¹ in 1916, reported an increase in the blood urea and diminution of phenolsulphonephthalein excretion in many cases of pneumonia and some other febrile conditions. In epidemic meningitis they found no changes in these tests for renal function. They did not separate carefully, however, the cases that showed evidence of acute nephritis from those that did not.

In this work the renal function of cases during and just after an acute infection was studied by the phenolsulphonephthalein test,² the estimation of blood urea,³ and the determination of McLean's⁴ index of urea excretion. In addition, evidence of renal irritation was sought for by examination of the urine for albumin, red blood cells and casts. Usually all the tests were performed on the same day. Occasionally the phenolsulphonephthalein test or the urine examination was done on the day following the urea determinations. Cases were selected among young people who presented no evidence of chronic nephritis and no evidence of acute nephritis as sought for by the usual urinary studies. The results have been grouped by diseases and recorded in tables with an accompanying discussion of the findings.

3 Van Slyke, D. D., and Cullen, G. E. *Jour Biol Chem*, 1914, **19**, 211

4 McLean, F. C. *Jour Am Med Assn*, 1916, **66**, 415

5 O'Hare, J. P. *THE ARCHIVES INT MED*, 1916, **17**, 711

6 Hedinger, M., and Schlayer. *Deutsch Arch f klin Med*, 1910-1911, **114**, 120

7 Tileston, W., and Comfort, C. W., Jr. *THE ARCHIVES INT MED*, 1914, **14**, 620

Technic — The phenolsulphonephthalein was injected intramuscularly as originally described by Rowntree and Geraghty and the urine collected after the first and second hour. The total for the two hours is recorded. This test and the examination of the urine were made for me by the house staff of the hospital, and to them I am indebted. At this hospital an excretion in two hours of 50 per cent of the phenolsulphonephthalein injected is considered normal. In estimating the index of nitrogen excretion the urine was collected over a period of two hours between 8 and 10 a m. One-half hour before this the patient was given about 200 cc of water. At 9 a m the blood was collected from a vein and prevented from clotting by oxalate crystals. The urea nitrogen was determined in the blood and urine by means of the urease method described by Van Slyke and Cullen³. In this hospital the blood urea nitrogen is considered normal when it falls between 10 and 20 mg per 100 cc of blood. The ammonia in the urine was determined according to the method used by the same authors. In a few of the cases in which the urine could not be collected exactly at the end of two hours, it was collected as soon after as possible and proper allowances made in estimating the twenty-four-hour quantity. Just what should be considered a normal index of urea excretion is difficult to decide, but the normal probably falls between 70 and 170 per cent.

TABLE 1—TYPHOID FEVER

Hosp No	Age	Date	Temp	Blood Urea, Mg per 100 C c	O	D	Index per Cent	Phthal per Cent 2 Hrs	Urine		
									Alb	Casts	R B C
5688	13	12/ 2/16	101.5	10.25	13.4	20.1	67	66	0	0	0
		12/19/16	Normal	11.18	13.6	15.5	170	60	0	0	0
5311	26	10/ 3/16	103.5	14.9	31.8	36.71	294		VSTr	0	0
		12/ 9/16	Normal	8.39	3.02	11.02	126	40	0	0	0
5487	18	10/27/16	103.0	11.42	25.6	15.36	272	53	SPTr	0	0
		11/18/16	Normal	10.95	2.68	8.95	58	75	0	0	0
5337	15	10/ 3/16	103.4	6.5	5.01	13.73	287		VSTr	0	0
		11/ 4/16	Normal	7.9	6.18	4.38	72		SPTr	0	0
5738	20	12/12/16	101.0	8.6	20.82	29.15	530	45	0	0	0
		12/21/16	Normal	12.78	6.48	20.22	108	67	SPTr	0	0
5568	27	11/11/16	101.0	6.9	6.7	6.27	135	58	Trace	0	0
		12/ 9/16	Normal	8.2	4.66	12.58	184	70	0	0	0

In Table 1 are recorded the studies on six cases of typhoid fever. There was no reason to suspect any disturbance of the kidneys in these cases and the examination of the urine showed no evidence of renal irritation except for traces of albumin in some of the cases. The second set of studies for renal function in these cases was not made until the temperature had been normal for a week or more. In those cases in which the elimination of phenolsulphonephthalein was studied it is seen that in three of the four cases it was lower during the fever than after, yet all the readings were within what we call normal limits. In the other case the phenolsulphonephthalein output was higher during the fever than after. The blood urea remained within normal limits both during and after the fever. In some cases it was slightly higher during the febrile period than after, but this variation was not consistent, for in other cases the blood urea was lower during the fever than

after All of these patients were on a high caloric diet, which they were taking well during the course of the fever. The index of urea excretion, on the other hand, in five of the six cases during the fever, was considerably elevated above the normal and above what it was in the same case after the temperature had fallen. The indexes of excretion when the temperature was normal fell within the rather wide limits allowed for normal, although some were at the lower end and others at the upper edge of the limits. The sixth case showed practically normal indexes during and after the fever, with the index somewhat higher after the temperature was normal. This was apparently as typical a case of typhoid as the other and no reason for the variation from the other cases was suggested.

In these tables the amount of urea estimated for the twenty-four hours, called "D," and the concentration of the urea in the urine, called "C," are also included. The cause for these high indexes during fever is apparently not due to constant variations in any one of the factors

TABLE 2—PNEUMONIA, TYPL I

Hosp No	Age	Date	Temp	Blood Urea, Mg per 100 Cc	O	D	Index per Cent	Phthal per Cent 2 Hrs	Urine			
									Alb	Casts	R	B C
5720	28	12/ 7/16	103.0	10.25	12.72	22.9	270	83	Sl tr	Many		0
		12/19/16	Normal	12.58	9.2	17.88	150	55	0	0		0
6095	42	2/ 8/17	100.0	36.12	31.5	32.4	18	52	Sl tr	Many		0
		2/20/17	Normal	16.6	23.32	22.38	127		0	0		0
5930	25	1/11/16	102.5	29.6	26.64	27.07	59	60	Trace	Few		0
		1/18/16	Normal	14.9	20.27	21.89	169	55	0	0		0
5567	39	11/ 9/16	103.0	16.3	34.6	19.03	183	55	Sl tr	Few		0

used in its estimation, so that one is unable to say that the high index was due to a constantly low blood urea, or high concentration of the urea in the urine, or increased total quantity of urea. The main feature is that most of these cases put out either a larger amount of urea during fever than after or else in a considerably more concentrated form in proportion to its concentration in the blood.

In Table 2 are recorded four cases of pneumonia which were classified in Group 1 of Cole's⁸ classification for pneumococci. These four cases showed evidence of renal irritation by the presence of albumin and casts in the urine during the fever. In the two cases in which the phenolsulphonephthalein test was studied during and after the fever, it showed a better excretion during the fever than after and was quite elevated in one of the cases. In the other two cases in which the phenol-

⁸ Cole's Classification. Dochez, A. R., and Gillespie, L. J. Jour. Am. Med. Assn., 1913, **61**, 727.

sulphonephthalein excretion was studied only during the fever, the output was also normal. Two of the cases showed an elevated blood urea nitrogen during the fever. One of these had been given the specific antipneumococcus serum the night before, the other had not. The index of urea excretion in two of these cases was low during the fever and returned to normal after. In one of the other cases in which the blood urea was normal the index was elevated during the fever and returned to normal in convalescence. In the fourth case the blood urea was normal and the index was at the upper end of normal limits during the fever. This patient (5567) developed an empyema and subsequent study in the afebrile period was not done. In the two cases with the low index during the fever the output and concentration of the urea in the urine was quite high, but not enough so in proportion to the blood urea to keep the index normal. There was no constant variation in the relation of "C," "D" and the blood urea in the cases with the high indexes.

TABLE 3—PNEUMONIA, TYPE IV

Hosp No	Age	Date	Temp	Blood Urea, Mg per 100 C c	O	D	Index per Cent	Phthal per Cent 2 Hrs	Urine		
									Alb	Casts	R B O
5553	33	11/ 7/16 11/18/16	104 0 Normal	8 16 11 18	4 24 5 63	15 77 10 13	221 86	50 70	Sl tr SPTTr	Rare 0	0 0
5829	38	12/27/16 1/11/17	104 0 Normal	12 68 15 84	18 66 10 9	32 02 20 27	208 104		SPTTr 0	0 0	0 0
5940	15	1/13/17 1/30/17	103 0 Normal	12 68 20 7	19 35 13 33	56 89 15 2	640 54	70 15	VSTr 0	Many 0	0 0
5946	20	1/13/17 2/ 1/17	101 0 Normal	25 96 17 7	47 25 8 17	42 6 17 3	135 53	55 50	Trace 0	Num 0	0 0
6205	23	2/27/17 3/ 6/17	100 5 Normal	13 37 14 45	22 4 16 18	9 44 16 12	96 116	55 59	SPTTr SPTTr	0 0	0 Many
5817	45	12/23/16 Died	102 0	22 83	17 98	32 36	105	45	VSTr	0	0

In Table 3 are recorded six cases of pneumonia which belong to Group IV of Cole's classification. Several of these cases show evidence of renal irritation during the febrile period, as evidenced by the presence of albumin and casts in the urine. In these cases during and after the fever, the phenolsulphonephthalein elimination was within normal limits except in two instances, when it was only just below the normal. In two of these cases there was considerable variation in the phenolsulphonephthalein elimination during the febrile period from that after the fever had subsided. In one of the cases (5553), however, the elimination was more after the fever, in the other (5940) the excretion was more during the fever. The blood urea was slightly elevated during the fever in two of the cases. In these two cases, however, the index of urea excretion was normal. In three other of these six cases, however, during the fever the index of urea excretion was elevated,

and in one of them markedly so. In the five cases which recovered, the indexes of urea excretion were normal after the fever except in two. These two showed a moderate diminution of the index down nearly to 50 per cent. It is interesting to note that in one of these cases the index had been exceptionally high during the fever, and this suggests the possibility of fatigue appearing after the excessive activity. In the one case in which the patient died, the index of excretion was normal during the fever. The relations between "C," "D" and the blood urea do not show any constant variations to account for the variation in the indices.

In Table 4 are recorded five cases of acute articular rheumatism, in three of which (6203, 6256 and 6222) acute joint symptoms were present. In the other two (5774 and 6381) the joint symptoms had subsided a few days before and the fever was due to cardiac complications. The evidence of renal irritation, from an examination of the urine in all of these cases, did not exist except for possibly very slight

TABLE 4—ACUTE ARTICULAR RHEUMATISM

Hosp No	Age	Date	Temp	Blood Urea, Mg per 100 C c	C	D	Index per Cent	Phthal per Cent 2 Hrs	Urine		
									Alb	Casts	R B C
6203	24	2/27/17	101.0	19.34	15.74	26.39	76	50	VSTr	0	0
		3/ 8/17	Normal	17.71	10.83	11.17	33	40			
6256	28	3/ 8/17	100.0	18.17	23.6	31.72	162		0	0	0
		3/15/17	Normal	20.22	17.53	27.78	98	52	0	0	0
6222	32	3/ 1/17	100.0	16.31	29.32	31.66	192	54	VSTr	Occ	0
		3/22/17	Normal	17.7	19.3	29.60	139	44	0	0	0
5774	13	12/30/16	100.5	15.47	46.31	29.41	357	35	SPTr	0	0
		1/25/17	Normal to 99.0	9.32	5.05	11.8	129	50	0	0	0
6381	16	4/ 5/17	100.0	15.38	40.1	38.0	427	67	VSTr	Rare	0
		5/ 4/17	Normal	9.7	13.46	18.1	205	72	0	0	0

irritation in Cases 6222 and 6381. In only one of these cases was the phenolsulphonephthalein output below normal during the fever. In two others it was below normal after the temperature had returned to normal. In all the cases the blood urea nitrogen was practically normal during and after the fever without any consistent variation between the two periods. In one of these cases the index of urea excretion was at the lower limits of normal during the fever, but this same case showed the index still lower after the fever. In the four other cases the index during the febrile period was toward the upper limits of normal in the two without symptoms and considerably elevated in the two with cardiac complications. In one of the cases with cardiac symptoms the index remained considerably elevated after the temperature was normal. In the other cases it became normal after the fever except in the one case already mentioned, in which it fell below

normal As in the other group, there are no consistent variations in the "C" or "D" or the blood urea content to account for variation in the index

In Table 5 are grouped together a few cases of acute infection of various sorts Although in two of these cases (6247 and 6009) there was some evidence of renal involvement, they were included for comparison In the diphtheria case the interesting points to be noted are the increased index of urea excretion during the fever and the slight diminution of phenolsulphonephthalein excretion after the temperature had reached normal Otherwise the tests were normal

In the case of gonorrheal arthritis, the index of urea excretion was considerably increased during the febrile period and in the second test

TABLE 5—MISCELLANEOUS

Hosp No	Age	Date	Temp	Blood Urea, Mg per 100 Cc	C	D	Index per Cent	Phthal per Cent 2 Hrs	Urine			Comments
									Alb	Castrs	R B C	
5630	20	11/21/16 12/ 5/16	99.5 Normal	16.3 12.58	29.23 4.3	43.85 20.38	297 97	65 40	VSTr 0	0 0	0 0	Diphtheria serum given 11/20/16
5687	23	12/12/16 12/23/16	99-101 Nor -100	9.55 10.95	24.52 18.0	36.78 32.4	500 374	67 58	0 0	0 0	0 0	Gonorrheal arthritis
5888	30	1/ 6/17 2/ 1/17	103.5 Normal	12.16 16.96	21.4 2.5	29.5 14.1	254 24		0 0	0 0	0 0	Abcess periosteum
6151	43	2/17/17 3/ 1/17	100.0 Normal	24.7 16.54	30.28 13.72	30.88 16.46	44 36	50 21	0 0	0 Rare	0 0	Acute gout, obese
6247	19	3/ 6/17	102.0	21.44	14.36	8.96	21	41	Trace	0	Some	Cervical adenitis following tonsillitis
6247		3/10/17	Normal	13.42	12.9	11.61	69	40	VSTr	0	0	Acute nephritis
6009	26	1/23/17 2/13/17	102.0 Normal	54.5 16.35	16.5 3.55	23.43 16.61	9 41	0 50	VSTr 0	0 Many	Few 0	Bronehopneumonia Acute nephritis

it was still quite elevated It is only fair to say, however, that at this time the temperature still showed a slight afternoon elevation at times

The index of urea excretion during the febrile period in the case which showed an abscess of the periosteum was quite elevated, and after the fever was unusually low Unfortunately in this case the phenolsulphonephthalein elimination was not completed

In the patient with acute gout and obesity, although the phenolsulphonephthalein elimination was normal during the fever, it became lowered considerably after the febrile period The index of urea excretion was below the normal in both examinations

The case of cervical adenitis which from the urine examination and clinical picture suggested some renal involvement, showed a phenolsulphonephthalein excretion which was persistently slightly below normal during the fever and after The index of urea excretion also was considerably lowered during the fever but returned practically to normal after the fever

In the case of severe bronchopneumonia with clinical evidence of renal involvement, the phenolsulphonephthalein elimination was nothing and the index of urea excretion was very low. In convalescence the phenolsulphonephthalein elimination returned to normal but the index of urea excretion only returned toward normal, still remaining lowered. In this case during the febrile period the blood urea was considerably increased in amount.

These last two cases are of interest in that they show that any renal involvement which tends to disturb the functional tests more than offsets any tendency for the index of urea excretion to be elevated, as has been noted to occur in many instances during the febrile period.

It is evident from glancing at these tables that in the cases of acute infection in which there is no evidence of serious renal involvement, there is no constant impairment of renal function, as shown by these tests, either during or after the acute stage of the infection has passed. In some of the cases in the various diseases certain suggestions of impairment of function occur but not consistently enough to draw any definite conclusions. Thus, in the group of pneumonia cases of Type I the blood urea was elevated in two cases during the fever and the index of excretion lowered in these cases. In one case of pneumonia Type IV, the renal function was slightly below the average in two of the tests after the fever in a case in which the function had been especially active during the fever. Also, in one of the cases of rheumatic fever the function as shown by the index and phenolsulphonephthalein was below normal after the fever. In this case there had been no increase in function during the fever. On the other hand the striking feature about many of these cases in all the groups was the frequency of an abnormally high index of urea excretion during the course of the fever. As this increase in the index was not associated with an increase in the phenolsulphonephthalein excretion or an abnormally low blood urea, in most of these cases it seems more likely that it depends on some factors peculiar to fever which affect this test rather than to a hyperactivity of the kidneys during fever. Just what the factors are which caused this high index are not made clear by this study.

From these studies it may be concluded that these tests for renal function, namely, the phenolsulphonephthalein elimination, the urea nitrogen in the blood, and the index of urea elimination, failed to show consistent evidence of impaired renal function during the course of or following these acute infections in which the clinical picture or the urinary examination by the older methods showed nothing suggestive of acute nephritis.

Peter Bent Brigham Hospital

ALKAPTONURIA

S S SCHOCHET, M D
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The occurrence of alkaptonuria is sufficiently rare to justify the publication of the following case. Only nine of the seventy or so recorded cases of alkaptonuria have been reported occurring in the states.

As the exact cause of this condition is still unknown and as relatively few cases have been reported, it seemed well to add this record to those which have been published, with the findings and result of treatment. Fromherz has recently expressed the opinion that many alkaptonurics remained unnoticed, and he calls attention to the fact that forty-five of the seventy cases have been reported within the last fifteen years.

The term alkaptone (from *alkali* and *ἀπτείν*, "to absorb greedily") was first ascribed by Bodeker in 1857 to a substance found in the urine of a patient, which possessed two chief characteristics: first, the power to reduce alkaline copper solutions, and secondly, the property of absorbing oxygen from the atmosphere in the presence of alkali, and as a result turning to a brown-black color.

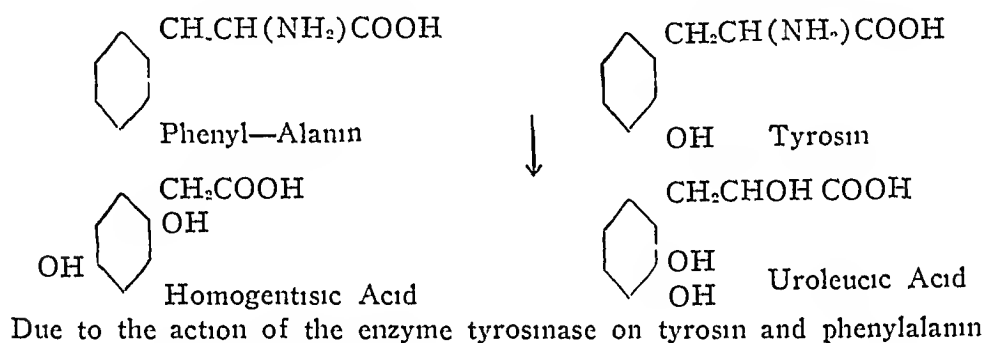
The urine may be clear and of normal color when passed, but later becomes of a dark brown and finally black color on exposure to the air. This condition may be present in cases of ochronosis, but is not a necessary accompaniment of this affection. Gouget has found a number of references in the literature of the past to cases of melanuria which were probably instances of alkaptonuria. Thus, Scribonius (1584), Zacutus and Lusitances (1649) describe cases of young children in apparent health who passed black urine, and Scheneck (1609) reports the case of a Monk who presented the same urinary anomaly during his whole life.

In 1875 Ebstein and Muller obtained a substance from the urine of an alkaptonuric patient by treating the urine with alcohol-ether, which formed the reactions given by pyrocatechin. This observation was of interest because it was the first case in which the opinion had been expressed as to what the reactions in alkaptonuria were. Fleischer next observed a urine which gave similar reactions with those of Furbinger in which he was able to demonstrate small quantities of pyrocatechin. Bodeker in a communication to Furbinger expresses the view that his alkaptone bodies might be similar to pyrocatechin.

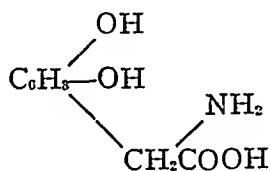
* Submitted for publication April 9, 1918

About this date Baumann reported that pyrocatechin is a normal constituent of horses' urine, and that frequently, if not regularly, is present in varying amounts in human urine

An excess of excretion of the normal constituent of pyrocatechin in the urine led many to the belief that it was identical with alkaptonuria. This view was expressed by Salkowski and Leube, who said "Apparently identical with pyrocatechin is the alkaptone of Bodeker and Fuibinger." The opinion has been expressed of late that homogentisic acid (hydroquinon-acetic acid), which is apparently derived from tyrosin, is a normal intermediary product in the destruction of tyrosin and phenylalanin, that its formation represents an oxidation which precedes the breaking up of the benzene ring, and that its appearance in the urine is an expression of metabolic insufficiency which renders the destruction of the benzene ring impossible



In 1886 and 1889 Kirk made a further contribution to our knowledge regarding alkaptonuria. The report is of interest chiefly because it is the first instance recorded in which the urine of more than one member of a family presented the characteristics of alkaptonuria. The opinion was conveyed that the condition may be congenital and occur in the offspring of consanguineous marriages. To Baumann and Wolkow we are indebted for the most exhaustive study of the subject of alkaptonuria. They were able to obtain the "alkaptone" in pure form, to ascertain its constitution, and to determine its derivation as a product of tissue metabolism. From the urine they isolated in pure form homogentisic acid, which has the following formula



It crystalizes in the form of large, transparent, prismatic crystals, which melt at 146.5 to 147 C and become yellow when free from water. They are not hygroscopic, and are soluble in water, ether, chloroform, benzene and in toluol. The authors draw comparisons

between homogentisic acid and the glycosuric acid of Marshall and the urolencinic acid of Kirk, showing the marked similarity in constitution

Embden studied another case of alkaptonuria and concludes as a result of his work, first, that we know nothing definite as to the etiology or place of formation of the homogentisic acid, and secondly, that the evidence that homogentisic acid is derived from tyrosin in the intestine as a result of the action of micro-organisms is rather against than for this view

As to treatment, there is nothing to be done, as the condition is of no pathologic significance Alkaptonuria is of importance, however, owing to the liability of its being mistaken for glycosuria The negative results with bismuth ferrocyanid and the polariscopic tests should at once rule out glycosuria

REPORT OF CASE

History—The case here recorded occurred in a male patient, aged 32, married, the father of two healthy children (the urine of these were normal) There was no history of alkaptonuria in the family The patient was a civil engineer, but was employed as a chemist for the previous two years

Present Illness—Complained of passing black urine, with periodic attacks of urticaria

Previous Illness—Had herpes zoster fifteen years prior to this consultation He denied all genito-urinary infection

Examination—The patient was a well developed, muscular, white man, height, 5 feet 8 inches, weight, 162 pounds

Eyes Reflexes normal, ophthalmoscopic examination negative, no abnormal pigmentation of retina

Heart and chest and abdomen were normal

The physical findings were negative except for the passage of a brown-black urine

The Wassermann reaction before treatment was negative, after administration of large doses of potassium iodid (40 to 60 grains three times a day) there was a four plus reaction

The Urine Physical Properties—Appearance When fresh, the urine was a light brown color, at times clear and free from sediment

Color On standing the urine perceptibly darkened, and this change was the more pronounced the longer the urine was exposed to the air, until it became of an inky black color Fleischer says it is at first, almost black, later brown by reflected light This condition was not determined

Odor There was a peculiar and slightly aromatic odor when freshly voided

Volume From the statements of other writers many alkaptonurics excrete either an excessive or deficient quantity of urine Some of the patients had other maladies, for this reason, perhaps, these divergencies from the normal are of no particular significance as far as alkaptonuria is concerned In the following instances the quantity of urine was less than 1,000 cc Furbringer's case, quantity small, average 600 cc, Brunne's, 900 cc, Ogden's, 974 cc, and Moraczewski's, 500 to 1,200 cc, and later 200 to 400 cc, Stier's, 360 to 1,030 cc, Hirsch's 700 cc, Garrod's, scanty and highly concentrated On the other hand, the following observers have reported quantities exceeding 2,000 cc, namely, Garner and Voirin, 2,000 to 4,000 cc, Stange, 1,000 to 4,000 cc However, more instances of deficient than excessive quantities seem to have been recorded In my case 1,400 cc was the average

Specific Gravity The specific gravity of alkaptonuric urine in several instances appears to have been high. Urines ranging from 1.020 to 1.025 have been recorded by Furbringer, Armstrong, Smith, Brune, Noccioi and Donsencii and Hammarstein and Schumm. In my case there was a specific gravity of 1.021.

Chemical Properties—Acidity I did not attempt to determine the acidity of the urine quantitatively, but merely tested each sample with litmus paper and found it to be decidedly acid. Alkaptonuric urine seems to retain its acidity for a considerable time on standing.

Fermentation, sugar, albumin, blood and blood pigments were absent.

Copper Tests Alkaptonuric urine will reduce Fehling's solution only on being heated, but to no extent with a cold solution. Supernated alkali solution on the urine produced a black zone but no precipitate (sodium hydroxid 10 per cent).

Spectroscopic examination was negative for bands due to iron.

Clinical Analysis—Alkaptonuria must be differentiated from the hemoglobinurias due to drugs (phenols) and diseases (malaria, etc.) by the presence of hemoglobin in the urine, from the melanurias and hematorporphyrinurias, and especially from the condition known as "paroxysmal hemoglobinuria frigore," by chemical and spectroscopic tests for the pigments.

As no treatment has been indicated in the various textbooks, at the suggestion of Dr. Schultz I attempted to unite the benzene ring of alkaptone with the benzoates, but with negative results. After continued failure to relieve the patient of his black urine, and in spite of a negative Wassermann I administered large doses of potassium iodid (from 40 to 80 grains, increasing to 100 grains three times a day). At the end of three days the patient had a severe iodid rash, and at the end of two weeks' treatment (modified) the urine became normal in physical appearance and in its chemical composition. Another blood test was made which showed a strongly positive Wassermann (4+). I doubted the specificity and accuracy of the test and two specimens of blood were submitted to Dr. Benjamin Gruskin of the Medical Research Laboratory and to Dr. Fischer. Reports of four plus Wassermann were returned for each specimen. I then administered 10 grains of tyrosin and twenty-four hours later submitted new specimens. The reports from these two laboratories and my own test showed a negative Wassermann. Therefore, the patient twenty-four hours after the administration of 10 grains of tyrosin turned a fully four plus Wassermann reaction into a fully negative one.

In a hasty review of the literature on the Wassermann reaction I found a somewhat similar condition reported by Soderbergh in which a strongly positive Wassermann reaction was converted by the administration of sodium bicarbonate and tyrosin into a negative test.

A further note on this phase will be published in a separate communication.

I had delayed the report of this case until the present time in the hope that a more complete study could be made, but in view of the fact that I am on active service with the colors in France and no opportunity for continued work along this line is possible at present, I wish to make this preliminary report.

I beg to acknowledge my indebtedness to Dr. Solomon Strauss for confirmation of my chemical findings and to Dr. Schultz of the Michael Reese Research Institute for many helpful suggestions in this study.

OCCLUSION OF THE ENTIRE INFERIOR VENA CAVA BY HYPERNEPHROMA, WITH THROMBOSIS OF THE HEPATIC VEIN AND ITS BRANCHES

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Although renal hypernephroma is of relatively frequent occurrence and metastasis by way of the venous system the usual mode of dissemination of the tumor tissue, it is rare to find extensive growth into the inferior vena cava and rarer still to have an intravascular hypernephroma occlude this vessel in its entire length and extend into the right chambers of the heart

In the present instance we have the unique picture of occlusion of the entire inferior vena cava from a hypernephroma growing along the left renal vein, completely filling the inferior vena cava from the iliac bifurcation to the right auricle, with the tumor mass extending through the tricuspid orifice into the right ventricle. The hepatic veins were thrombosed. There was acute central necrosis of the liver and death in acidosis.

REPORT OF CASE

History—The patient, a man aged 63, entered the medical service of the Peter Bent Brigham Hospital, Jan 22, 1917 (Med No 11605), complaining of swelling of the feet, legs and scrotum, shortness of breath, loss of appetite, and "gas on stomach." At that time the following history was obtained. He had been a druggist for forty years and quit work but two days previous to entrance. His appetite had been fairly good prior to the last six months, bowels were always regular and he had never had jaundice, colic, vomiting or other gastro-intestinal symptoms. Hematuria had never been noticed. His weight had suffered considerably the previous six months. In September, 1916, he weighed 184 pounds and on entrance to the hospital only 113 pounds. He said the marked loss of weight was due to his poor appetite.

After returning from his vacation in September, 1916, he noticed that his appetite was failing, and soon he began to have eructations of gas after eating. During the last three months he could not eat as much as previously because he felt "filled up" and at times, but not frequently, he regurgitated a little food. He gradually decreased the amount eaten at a meal but did not eliminate any elements of his diet. There was distress and sense of fullness in the epigastrium after meals.

Three weeks before admission he noticed for the first time that his legs and scrotum were slightly swollen, more so at night. A physician told him

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* From the Medical Clinic and Pathological Laboratory of the Peter Bent Brigham Hospital.

his urine contained a little albumin and he was warned against "kidney trouble" Digitalis, taken for two weeks, caused no improvement in the swelling Ten days later another physician prescribed gentian and iron, with the result that his appetite increased There was then marked shortness of breath on exertion, gradually increasing, but not sufficient to keep him from work Three days before admission his urine was examined but no albumin was found He was advised to enter the hospital to rest up

Physical Examination—At entrance this showed the patient well developed and fairly well nourished, complaining of the coldness of the ward His skin was white and covered with dry, oily scales His thorax was long, narrow and rather full The respiratory movements were normal The cardiac impulse was in the fifth interspace, 13 cm to the left of the midsternal line, the left border 15 cm out in the fifth interspace, the right border 3.5 cm to the right of the midsternal line, the upper border at the third rib At the apex the sounds were slow and regular, the first sound sharp and preceded by a soft presystolic murmur and followed by a long, blowing diastolic murmur which was transmitted into the axilla A short systolic murmur was heard in the aortic area, loudest in the second right interspace and not transmitted The peripheral vessels were tortuous and easily palpated There was a Corrigan pulse but no Duroziez' sign

In the lungs were many fine crackling râles along the lower borders The abdomen was scaphoid and there was shifting dullness in the flanks There was a sense of resistance in the epigastrium, but no definite mass was felt, nor were there any areas of tenderness The liver dullness extended from the fifth rib to the costal margin The spleen and kidneys could not be felt The penis and scrotum were edematous The legs showed moderate soft edema

Clinical Pathology—Hemoglobin (Sahli), 63 per cent, erythrocytes, 3,700,000 Smear showed no abnormal forms The urine contained a slight trace of albumin and a moderate number of hyaline casts The phenolsulphonephthalein output was 42 per cent in two hours Clinical diagnosis, chronic cardiac valvular disease, aortic insufficiency, syphilitic aortitis (?), secondary anemia, chronic nephritis He was given digitalis leaves, 0.1 gm four times a day

The following day a capillary pulse was noted in his finger nails January 29, temperature, pulse and respiration were normal After twelve doses of 0.1 gm digitalis leaves, diuresis occurred with a loss of 6.4 kg The blood Wassermann reaction was double plus Gastric analysis showed anacidity The edema of the extremities was much decreased but had not entirely disappeared

February 6 Roentgen report "Negative gastro-intestinal findings In the gallbladder region there is a suggestive shadow, but not sufficient to be due to a calculus"

February 12 The urine contained the slightest possible trace of albumin but no erythrocytes or casts He had lost 12 pounds in weight and complained of "weakness of stomach" He would have liked to eat more but could not His speech was rambling

February 14 Edema was more marked in the right leg than in the left The glands in the right groin were enlarged and tender The right saphenous vein for one third the distance to the knee was very tender Apparently thrombosis of the saphenous vein could account for the unilateral edema

February 20 Blood pressure systolic 150, diastolic 80

February 23 The abdominal veins were enlarged, the blood flowing from below upward There was marked edema of the right leg and slight edema of the left leg The abdomen was rather full, especially the upper part No masses were felt The signs were those of obstructed inferior vena cava

February 27 Blood pressure systolic 130, diastolic 80

April 2 Blood pressure systolic 140, diastolic 80

April 4 There was a definite fluid wave in the flanks The liver edge suddenly became palpable 9 cm below the costal margin in the right mammary

line He had a strong "acetone" breath and vomited frequently The respirations were of the character of acidosis

He later became comatose Alveolar air carbon dioxide tension 11.6 mm Hg, temperature 97 F He was given 3 per cent sodium bicarbonate in



Fig 1—Anterior view of authors' specimen

physiologic sodium chlorid solution per rectum by Murphy drip Catheter specimen of urine, 500 cc, showed a moderate amount of diacetic acid Shortly after 6 p m his respirations slowed down and stopped

Necropsy—Performed sixteen hours postmortem by Dr E W Goodpasture

Diagnoses—Hypernephroma of left kidney with invasion of left renal vein, inferior vena cava and one of right renal veins, occlusion of inferior vena cava, metastases to liver and lungs, multiple diverticuli of duodenum and jejunum, aortic arteriosclerosis, hypertrophy of heart, left, dilatation of aortic ring, congestion of liver, ascites and bilateral hydrothorax, edema, fatty degeneration of heart, bronchopneumonia

Body The body was that of a large framed, middle aged, white man, showing considerable emaciation. The tissues were flabby and there was considerable edema of extremities, the legs pitting easily on pressure. The thorax was barrel shaped, abdomen protuberant.

Peritoneal Cavity Contained 180 cc of clear yellow fluid, liver extended two fingers' breadth below the costal margin in the right mammary line, diaphragm on both sides at fourth interspace.

Thoracic Cavity Lungs were voluminous, each covered largely by thin, tough, fibrous adhesions, 300 cc clear yellow fluid in each pleural cavity.

Heart Enlarged, especially the left side, mitral ring measured 9 cm, aortic 8.25 cm, aortic valve was normal except for extensive thickening about the corpora astantia and glueing together and calcification between the posterior and right cusps, myocardium was very flabby and pale yellow, heart was left in situ because of necessity of careful dissection of inferior vena cava which was filled with tumor growth extending into the right auricle.

Lungs Voluminous, lateral portion of right lung and anterior portion of left lung were covered by fibrous adhesions. On the surface of each lung a great number of yellow, firm tumor nodules up to 2 cm in diameter, for the most part smaller, were scattered irregularly over the surface. On section similar tumors were found scattered throughout the lung substance. The tumor masses were rather opaque on the cut surface, very soft and grayish-yellow in color. Sometimes the centers were soft and yellow, while the peripheries were more translucent. A yellow opaque center was often surrounded by a red zone and the peripheral gray tissue appeared to be vascular.

Gastro-Intestinal Tract The duodenum was normal for 6 cm beyond the pylorus. At this point there was a diverticulum lying just over the head of the pancreas, 2.5 cm in diameter. Just opposite Treitz' ligament was another diverticulum measuring 2.5 cm in diameter, and 6 cm below was a very large diverticulum 5 cm in diameter. All opened into the intestine, as could be determined by squeezing air from them into the intestine. Beyond the largest were a dozen smaller in the fat of the mesenteric attachment for a distance of one foot.

Liver Larger than normal, dark purple. On section lobulation was distinct, centers purple, depressed, portal areas grayish yellow. The hepatic veins from the largest to the smallest were plugged with dark, purple thrombi. In the middle anterior portion of the left lobe a small mass was found measuring 5 mm, with a grayish pink center and yellowish periphery, which appeared to be a tumor metastasis.

Tumor A large mass occupying the region of the left kidney on section was found to be a hypernephroma occupying the upper two-thirds of the kidney substance. It measured 10 cm in length and 8 cm in width. The surface of the kidney in the region of the tumor was lobulated and the capsule was very vascular. On section through the tumor it presented a yellow, opaque surface composed of tissue resembling adrenal cortex. Numerous small hemorrhages were scattered throughout the tumor and there was a pink tone to the tumor tissue, indicating great vascularity. Brighter yellow opaque areas were scattered through the tumor which appeared to be areas of necrosis.

The right kidney was of normal size. The capsule was smooth, stripped easily, leaving a slightly irregular surface. The left renal vein was tremendous. It was plugged and distended with soft yellow tumor tissue, and measured 12 cm in length and 5.5 cm in diameter. The inferior vena cava was completely plugged with tumor growth both in the upper and lower portions from

the origin of this renal vein. In its upper portion, however, it was very greatly dilated, being 5.5 cm in diameter, the lower portion 3 cm in diameter, and became attenuated as the pelvis was approached. Both internal iliac veins were plugged with tumor thrombi. The tumor extended upward in the vena cava into the right auricle and ventricle, but the great distention of the vein

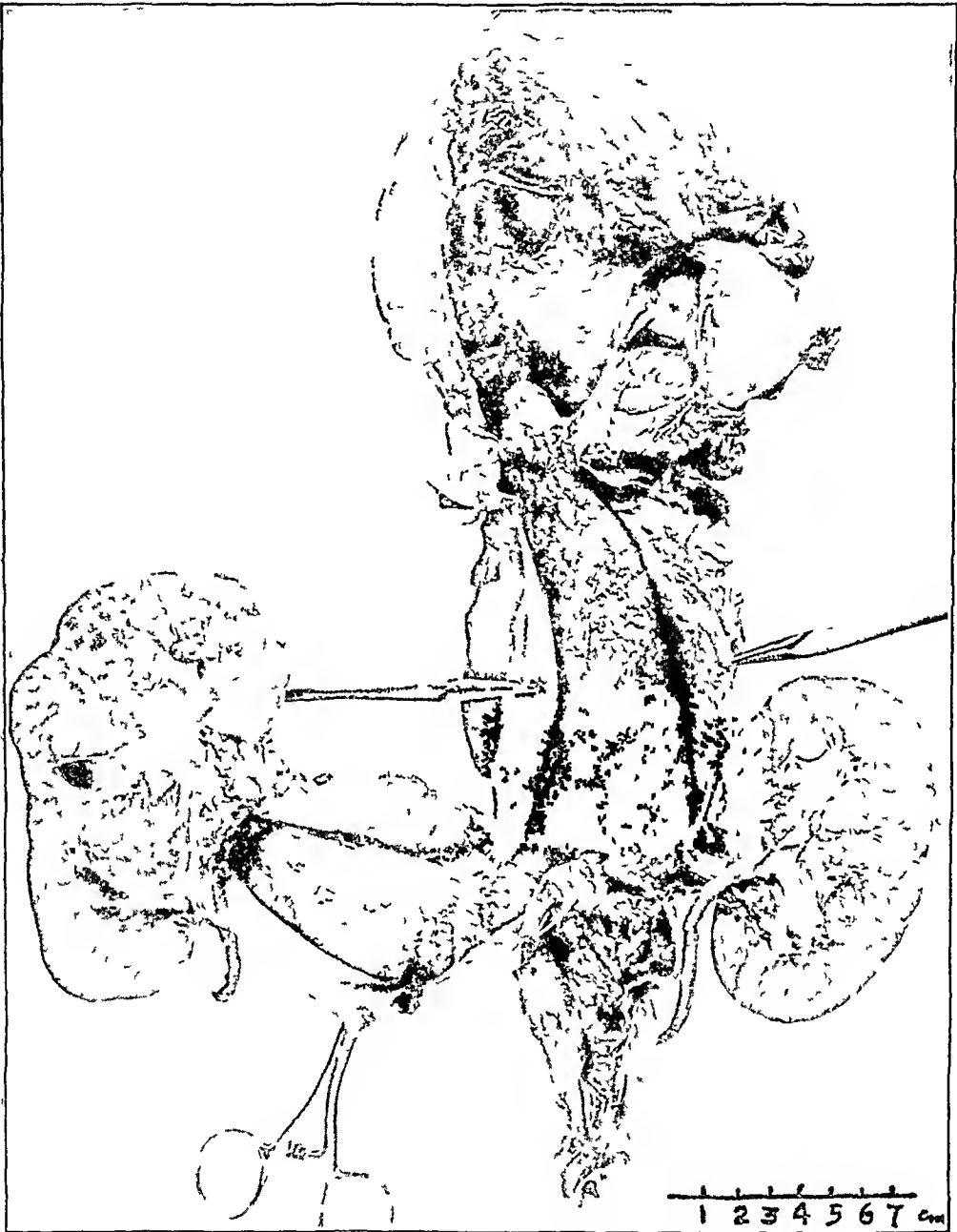


Fig 2—Posterior view of specimen

ended at the diaphragm. Above this point it measured 2.5 cm in width. The right renal veins were two in number and about normal in size. The superior vein, 1 cm in diameter, was patent in its entire length. The inferior right vein was 0.5 cm in width, deep purple and quite solid. The pelvis of each kidney and the ureters were normal.

Adrenals Normal in size and normal in general The left adrenal could be almost completely dissected out from the tumor about its superior surfaces, but inferiorly, next to the kidney, it was invaded by tumor mass and could not be separated from it The perirenal fat of the left kidney was very thick and firm On section this fat showed evident tumor extension in the connective tissue between the fat lobules, but the rigidity of the fat did not appear to be due entirely to tumor growth, but probably to connective tissue thickening between the fat lobules There was some fat of yellow, opaque appearance, rather than translucent

Pelvic Organs The vessels about the prostate were thrombosed

Microscopical Examination—**Left Kidney** The tumor is composed chiefly of polyhedral cells with pale or clear, vacuolated cytoplasm The nucleus, containing one or two basophilic nucleoli, is centrally or eccentrically placed The cells are arranged chiefly in alveolar form, but columnar formation is also present In some sections tubular architecture is strikingly predominant, strongly suggesting renal tubules There are many large and small vascular spaces lined with a single layer of flat epithelium and containing much blood There are many small thrombi undergoing hyalinization The tumor is not sharply marked off from the renal substance proper The cortex of the kidney shows much fibrosis and hyalinization of glomeruli and obliteration of the normal tubular arrangement Sections of the tumor from the renal pelvis show a less differentiated type and arrangement of the cells, the latter tending to be more spindle shaped than polyhedral

Right Kidney Chronic passive congestion and moderate amount of fatty change in convoluted tubules

Lung There are many scattered small nodules of tumor tissue which occupy alveoli, the walls of which are thickened There is marked chronic passive congestion

Spleen Shows chronic passive congestion

Liver There are obliterating thrombi in the tributaries of the hepatic veins and extensive central necrosis of the liver substance with hemorrhagic infiltration in the necrotic areas The normal columnar architecture is retained only at the peripheral portions of some of the lobules There is very little polymorphonuclear reaction within the areas of necrosis Sections of the thrombi from the hepatic veins show no tumor tissue, and the thrombi are apparently of recent origin, with the exception of one in the quadrate lobe in which organization has begun

Bone Marrow The bone marrow is hyperplastic

Thrombus Section of the thrombus from the inferior vena cava and right auricle show almost solid infiltration with tumor cells, with little tendency to any definite arrangement There is great variation in size, shape and intensity of staining of the individual cells

The thrombi from the right renal veins contain no tumor tissue

Sections of the thrombi occluding the caval orifices of the hepatic veins show no tumor tissue The thrombus in the vein draining the quadrate lobe shows beginning organization, those involving the right and left lobes are apparently about twenty-four hours old

Portions of the thrombus from 4 cm below the iliac bifurcation in the right and left common iliac veins contain a few strands of tumor cells, which, however, are more spindle-shaped and not vacuolated, corresponding more to the morphology of the tumor cells in the cardiac thrombus

In the left renal vein, just proximal to the caval orifice, sections of the tumor mass show a strikingly tubular arrangement of tumor cells, but no basement membrane was demonstrable with Mallory's phosphotungstic acid-hematoxylin stain

Pleasants,¹ in 1911, was able to collect 314 cases of obstruction of the inferior vena cava. Of this number 171 were due primarily to thrombosis, the majority of which were associated with inflammatory foci elsewhere in the body. Obstruction due to new growths (*Geschwulst-thrombose*) occurred 88 times, by invasion, 48, by pressure, 21, and by thrombosis, 19. Due to new growths in the kidney, 29 times, classified as follows: carcinoma, 21 times, causing invasion 12, pressure 2 and thrombosis 6 times; Sarcoma 8 times, causing invasion 5, pressure 2 and thrombosis 1 time. Due to new growth in the suprarenal gland, 3 times, sarcoma, 3 times, causing invasion 1, pressure 1, and thrombosis 1 time. Invasion was found to be most frequent in the middle third of the cava and the most common path of invasion was through the renal veins, and in an upward direction. Obstruction by pressure from without arose most frequently also in the middle third, owing to the nearness of the liver and other structures. Thrombosis was commonest in the lower third but also occurred in the upper and middle thirds through disease of the affluent veins.

Of the cases of *Geschwulst-thrombose*, in 43 cases accurately described, Pleasants found the lower third alone occluded in 9 cases and lower and middle thirds together in 7 cases, the middle third alone in 6 cases and the middle and upper thirds together in 17 cases. In only one instance was the entire cava from the iliacs to the right auricle filled. In 13 cases the growth reached as far as the right auricle or actually invaded it.

The most striking symptoms or physical signs of obstruction of the vena cava encountered were, lumbar pain, edema of the lower extremities and abdominal wall, and the establishment of collateral circulation. All of these features were found to depend on the position, extent, rapidity and completeness of the obstruction. The most strikingly developed of the superficial collateral circulatory routes was the superficial inferior epigastric-internal mammary channel. This was the collateral channel shown in our case. In many instances, with no superficial routes evident, the blood reaches the heart through deep vessels, the most frequent way being through the internal iliac-ascending lumbar-azygos-superior vena cava anastomosis.

There are several extraordinary features in our case. (a) The remarkable extension of the tumor from the upper pole of the left kidney to the left renal vein to the inferior vena cava which it traversed below as far as the iliac bifurcation and grew upward into the right auricle and right ventricle, causing mechanical embarrassment to the tricuspid valve. The nodules in the lungs were most likely derived from emboli from this portion of the tumor. Of the right renal veins

1 Pleasants. Johns Hopkins Hosp. Rep., 1911, 16, 363.

(there being two), the inferior one was distended with red thrombus extending in from the inferior vena cava as far as the renal pelvis. The orifices of the hepatic veins were plugged with the tumor and metastases were present in the liver substance. (b) The first noticeable symptoms occurred seven and one-half months before death. They were in the nature of loss of appetite, sense of fullness after eating and gastro-intestinal discomfort of more or less vague character. Edema of the legs and scrotum appeared five months later, during which time there was a loss in weight of 70 pounds. However, the patient was able to attend to his work right up to the time of his entrance to the hospital where he came merely to get "rested up." (c) The absence of hematuria. (d) The late appearance of definite signs of obstruction of the inferior vena cava in spite of the fact that that vessel was occluded in its entire length at necropsy. (e) The acute swelling and centro-acinous necrosis of the liver from thrombosis of the hepatic veins and death in acidosis. The sudden enlargement of the liver noted clinically was probably associated with the hepatic thrombosis.

Metastases in hypernephroma are frequently extensive. Growth of the tumor along the renal vein to the inferior vena cava from the affected kidney is not so common. Ribbert² in his *Geschwulst Lehre* mentions a case in which the tumor ascended the inferior vena cava to the right auricle without obstructing the hepatic veins. J. Israel³ and Rolleston⁴ have reported instances of invasion of the inferior cava, the latter's case being secondary carcinoma of the right suprarenal extending in along the capsular vein.

The remarkable patient of Parkes Weber⁵ showed symptoms of obstructed inferior vena cava, enlarged liver and spleen and ascites. The last two days there occurred anuria, uremia, coma and death. Necropsy disclosed a thrombus-containing tumor (papilliferous adrenal carcinoma) commencing in the left renal vein involving both renal veins, both hepatic veins, the whole of the inferior cava with the upper end projecting into a partially occluded right auricle. Both adrenals and kidneys were infiltrated with "malignant hypernephroma." Nodules of tumor were present in the liver and lungs. The liver also showed the central necrotic changes of extreme passive congestion. Death occurred from thrombosis of the better kidney with resultant anuria and uremia.

Herbert French⁶ has described a case of carcinoma of the left kidney with a continuous clot of tumorous tissue extending along the left renal

2 Ribbert *Geschwulste Lehre* 1904, p. 35

3 Israel *Deutsch Med Wchnschr* 1904, 30, 489

4 Rolleston and Marks *Am Jour Med Sc* 1898 116, 404

5 Weber Parkes *Proc Royal Soc.* 1915 8, 6

6 French *Tr Med Soc London* 1912 35, 243

vein, up the inferior vena cava into the right auricle, producing an intracardiac polypoid mass leading to tricuspid stenosis of the ball and socket type Rolleston⁷ quotes Adam¹ as having seen a similar extension of adrenal tumor

Other neoplasms, such as carcinoma and teratoma of the testis,⁸ have produced extensive deposits in the inferior vena cava Thrombosis may give rise to a similar train of symptoms from occlusion of the inferior cava, hepatic veins and extension into the right auricle

The symptoms produced by simple occlusion of the hepatic veins are not always very definite The syndrome of Craven Moore,⁹ progressive enlargement of the liver, signs of involvement of the inferior vena cava and ascites, is mentioned by Osler¹⁰ as being characteristic of stenosis of the orifices of the hepatic veins In Chiari's¹¹ three cases which had a luetic background, death occurred from ascites and pulmonary edema Winternitz¹² ligated an hepatic vein in a dog and observed no untoward effect or any macroscopic or microscopic changes in the liver

In our case, twenty four hours before death the liver suddenly became greatly enlarged, the patient developed symptoms of acute acidosis with strong "acetone" breath, alveolar air carbondioxid tension of 11.6 mm Hg, and diacetic acid was found in the urine The central necrosis of the liver lobules and the thrombi behind the tumor tissue in the orifices of the hepatic veins appeared to be about twenty-four hours old

The sudden enlargement of the liver coincident with the onset of acidosis suggests a point which may be of diagnostic significance in acute thrombosis of the hepatic veins, where there are already signs of obstruction of the inferior vena cava

The more rapid cases of hepatic obstruction give a picture which much resembles myocardial failure, there being present cyanosis, congestion of the lungs, enlarged tender liver, and ascites¹³ The rarity of thrombi in the hepatic ostia has been attributed to the marked obliquity of the veins and also to the diminished coagulability of the hepatic blood¹⁴

The structure of the tumor in our case is interesting in that the tubular arrangement of the cells is quite the predominating architecture in some sections and the individual cells are strikingly like those

7 Rolleston Diseases of Liver and Bile Ducts, 1912, p 498

8 McCallum Textbook of Pathology, 1916, p 1010

9 Craven Moore Med Chron Series 4, 1902, 3, 240

10 Osler The Principles and Practice of Medicine, 1915, 563

11 Chiari Zeigler's Beitr z Path Anat u z Allg Path, 1899, 26, 1

12 Winternitz Bull Johns Hopkins Hosp, 1911, 22, 396

13 Thompson and Turnbull, Quart Jour Med, 1912, 5, 277

14 Kretz Ergebn d allg Path, 1902, 8, 498

of normal renal tubules, being cuboidal and with granular cytoplasm instead of being vacuolated. There are all gradations between the cells of the normal kidney tubule and the more primitive, less differentiated, heavily fat-laden cell of typical hypernephroma.

SUMMARY

Occlusion of the inferior vena cava by new growth (*Geschwulstthrombose*) is rare, up to 1911 there having been but forty-three cases accurately described. In thirteen of these the growth reached as far as the right auricle or actually invaded it. In only one instance was the entire cava from iliacs to right auricle filled. Since then several other instances of obstruction by intravascular new growth have been reported, two of which showed occlusion from the level of the renal veins with tumor projecting into the right auricle. In one case the tumor tissue completely filled the inferior vena cava and extended into the right auricle.

The case reported here is one in which a renal hypernephroma extended from the kidney into the left renal vein, traversed the inferior vena cava below as far as the iliac bifurcation and grew upward into the right auricle and right ventricle causing mechanical embarrassment to the tricuspid valve.

The orifices of the hepatic veins were plugged with tumor and there was acute central necrosis of the liver from thrombosis of the hepatic vein and its branches. Sudden enlargement of the liver was accompanied by the onset of acidosis which persisted until the death of the patient twenty-four hours later.

Where there are already signs of obstruction of the inferior vena cava, sudden enlargement of the liver coincident with the onset of acidosis is probably indicative of acute thrombosis of the hepatic veins.

ALIMENTARY RENAL GLYCOSURIA

KINGO GOTO, M D

NEW YORK

INTRODUCTION

The glucose content of normal human urine is under 0.1 per cent, usually merely a trace. The kidneys normally excrete urine containing a lower concentration of glucose than is found in the blood. When the kidneys show a higher permeability for glucose, sugar should appear in the urine while the tissues still retain the normal power of utilizing dextrose. So-called "renal glycosuria" occurs on account of an abnormal permeability of the kidneys, without any disturbance of intermediary carbohydrate metabolism. In such a condition there are no diabetic symptoms and the blood sugar is normal.

The existence of this condition was first declared by Klempeier¹ at the Congress of Internal Medicine, in Berlin, 1896, and the conditions for its diagnosis were given as follows:

1 The glycosuria has almost no relation to the quantity of carbohydrate in the diet.

2 Not only is there no hyperglycemia, but sometimes even hypoglycemia.

3 When nephritis occurs the sugar in the urine diminishes or disappears.

Vo Noorden,² in his book, "Zuckerkrankheit," refused to recognize the cases of renal diabetes previously reported, and held that the condition had not been demonstrated. Allen,³ who recognizes renal glycosuria, in his book, "Glycosuria and Diabetes," says that "the name diabetes is unjustifiable, diabetic symptoms are absent, but those of nephritis, neurasthenia and malnutrition are frequent," and again, "almost always the glycosuria is very slight, a mere fraction of 1 per cent." Joslin⁴ recognized renal glycosuria and declared that an observation of several years was necessary for its diagnosis, clinical diagnosis without long observation of the patient being dangerous.

* Submitted for publication April 24, 1918.

* From the Hospital of the Rockefeller Institute for Medical Research.

1 Klempeier, G. Cong. Int. Med., Berlin, 1896. Ueber Regulatorische Glykosuria u. renalen Diabetes, Berl. klin. Wchnschr., 1896, **33**, 571.

2 Von Noorden, C. Die Zuckerkrankheit und ihre Behandlung, Ed. 6, Berlin, 1912, p. 37.

3 Allen, F. M. Glycosuria and Diabetes, 1913.

4 Joslin, E. P. Treatment of Diabetes Mellitus, 1917.

Since the initial report of Klemperer a few reports of cases have been made in Germany by Luthje,⁵ Bonninger⁶ Weiland⁷ Tachau⁸ Frank⁹ de Langen¹⁰ and Galambos¹¹ and in America recently by Lewis and Mosenthal¹² Murlin and Niles¹³ and Strouse¹⁴ The details of these reports will be included in the chapter of discussion

REPORT OF CASE

As renal glycosuria is considered rare observations on one case are here reported as follows

History—Man aged 33 Japanese physician No diabetic or neuropathic heredity, healthy childhood at the age of 22 the patient had typhoid fever in the course of which albumin and casts were found in the urine for about two weeks After university graduation in 1909 he was assistant at the university hospital He was healthy, no complaint of good nutrition, body weight, 50 kg, height, 161 cm Since 1911, his weight gradually increased to 54 kg there was increasing appetite, particularly for sweets, besides regular diet cakes containing about 50 to 70 gm of sugar were eaten once and sometimes twice in the afternoon In April 1913 after a meal consisting of 200 gm rice 150 gm meat, vegetables cooked with sugar after Japanese fashion and much candy an examination of the urine passed within two hours revealed 0.75 per cent sugar The determination of sugar in the urine was made qualitatively by the Almen-Nylander method, and quantitatively by Kumagawa and Suto's modification of Pavy's method On the following day after a lunch of 50 gm bread and tea, the urine showed a slight sugar reaction On the third day after keeping in the meantime to carbohydrate-free diet the urine showed no sugar reaction after a meal of 30 gm bread, but after a lunch of 60 gm bread, the glycosuria was present He considered himself diabetic and treated himself accordingly After eating 60 gm bread at one time sugar regularly appeared in the urine passed within two hours The percentage of sugar was always below 0.7

From June to November 1913 a diabetic diet was followed Sugar was excluded but about 30 gm carbohydrate in the form of bread and rice were taken with each meal, or from 90 to 100 gm daily The urine, examined

5 Luthje, H Beitrag zur Frage des renalen Diabetes, München med Wchnschr, 1901, **38**, 1471

6 Bonninger, M Beitrag zur Frage des Nierendiabetes, Deutsch med Wchnschr, 1908, **34**, 780

7 Weiland W Ueber einige ätiologisch bemerkenswerte Diabetesformen Deutsch Arch f klin Med, 1911 **102**, 167

8 Tachau, H Beitrag zum Studium des Nierendiabetes Deutsch Arch f klin Med, 1911 **104**, 448

9 Frank E Ueber experimentelle u klinische Glycosurien renalen Ursprungs Arch f exper Path u Pharmacol., 1913 **72**, 387 and 443

10 de Langen C D Beitrag zur Kasuistik des renalen Diabetes Berl klin Wchnschr 1914, **51**, 1792

11 Galambos A Ueber den renalen Diabetes, Deutsch med Wchnschr 1914, **40**, 1301

12 Lewis, D S, and Mosenthal, H O Renal Diabetes, Bull Johns Hopkins Hosp, 1916, **27**, 133

13 Murlin, J R and Niles W L Renal Glycosuria Am Jour Med Sc, 1917, **153**, 79

14 Strouse S Renal Diabetes Med Clinics of Chicago 1916, **2**, No 2, p 239

from time to time showed an occasional sugar reaction. From January, 1914, the strict diabetic diet was remitted, but no sugar was taken, the diet included from 150 to 200 gm carbohydrate daily, in the form of rice and vegetables. For a period of two years, the urine was not examined. Beginning April, 1916, after coming to America, sugar was added to the diet according to inclination, in the form of candy and ice cream. During this time the subject felt well and experienced no weakness. Sept 17, 1917, examination of the urine after the ordinary lunch showed almost 0.2 per cent sugar. The determination of sugar in the urine was made qualitatively and quantitatively by Benedict's method¹⁵. From September 20 to October 15, the diet consisted approximately of 100 gm fat, 150 gm carbohydrate, and from 150 to 200 gm protein per day. Sugar was excluded, the urine showed no sugar reaction. But on a free diet containing sugar the urine two hours after meals occasionally showed a slight sugar reaction, not more than 0.2 per cent. The urine volume was not increased, and no sugar reaction was seen with mixed twenty-four-hour urine.

Experimental—October 20, blood was taken at 9 a. m., before breakfast, after fasting over night, and determination of sugar in the blood made by the method of Lewis and Benedict,¹⁶ cholesterol in whole blood by Bloor's method,¹⁷ and carbon dioxide in the plasma by Van Slyke's method.¹⁸ All showed normal. The blood pressure was also normal.

TABLE 1—FINDINGS IN PLASMA AND WHOLE BLOOD
OCT 20, 1917, AT 9 P. M., BEFORE BREAKFAST,
AFTER FASTING OVER NIGHT

Sugar in Plasma, Per Cent	Cholesterol in Whole Blood, Gm per 100 C c	CO ₂ Capacity of Plasma, Vol Per Cent
0.11	0.22	74

From November 29, every morning a certain amount of carbohydrate was ingested after the night's fast, with results as follows. After 33 gm starch and 25 gm fat, no sugar appeared in the urine, but with increase of starch to 39 gm, sugar appeared one or two hours after meals, but in quantities so slight that it was hard to estimate its percentage by Benedict's quantitative method. Blood sugar was examined for every thirty minutes after meals, but no hyperglycemia appeared. After ingestion of 150 gm banana (34 gm carbohydrate), the urine showed sugar, presumably because of the sugar content of

¹⁵ Benedict, S. R. The Detection and Estimation of Glucose in Urine, Jour Am Med Assn, 1911, **57**, 1193.

¹⁶ Lewis, R. C., and Benedict, S. R. A Method for the Estimation of Sugar in Small Quantities of Blood, Jour Biol Chem, 1915, **20**, 61.

¹⁷ Bloor, W. R. The Determination of Cholesterol in Blood, Jour Biol Chem, 1916, **24**, 227. The Distribution of the Lipoids (Fat) in Human Blood, Jour Biol Chem, 1916, **25**, 577.

¹⁸ Van Slyke, D. D., Stillman, E., Cullen, G. E., and Fitz, R. Studies of Acidosis, Jour Biol Chem, 1917, **30**, No 2, p 289.

the banana After 50 gm oatmeal (34 gm carbohydrate), the urine showed sugar in two hours, but the blood sugar was normal After 150 gm potato (36 gm carbohydrate), there was glycosuria in one hour, but no hyperglycemia Therefore, after the ingestion of more than 34 gm carbohydrate, the urine showed sugar after meals, without regard to the kind of starch taken, while the blood sugar was always normal

In the third experiment (Table 3), large quantities of carbohydrate were ingested to determine the rise of blood sugar

After the ingestion of 130 gm rice (carbohydrate about 100 gm), the urine showed from 0.16 to 0.29 per cent sugar, which lasted to the fourth hour after meals The total sugar excreted amounted to 0.25 gm Blood sugar, which reached its maximum in the first hour, amounted only to 0.115 per cent No hyperglycemia was seen After ingestion of 200 gm starch, the urine showed from 0.2 to 0.3 per cent sugar which lasted for 2.5 hours The total amount of sugar excreted was 0.17 gm Blood sugar reaching its maximum in 2.5 hours was 0.145 per cent Sugar appeared in the urine after thirty minutes, when the blood sugar showed only 0.139 per cent

In the fourth experiment (Table 4), glucose was taken in various quantities, in the morning as in the former experiments

After 50 gm glucose, sugar appeared in the urine in 30 minutes to 1.5 hours, the total amount being 0.07 gm The maximum of blood sugar was 0.128 per cent, with return to normal at the end of the first hour After 100 gm glucose, sugar appeared in the urine at 30 minutes to 1.5 hours with a total amount of 0.9 gm, blood sugar reached its maximum at 0.164 per cent with return to normal within 3 hours After 200 gm glucose, sugar appeared after 30 minutes and lasted 4.5 hours, with a total excretion of 0.6 gm, the maximum of blood sugar was 0.175 per cent with return to normal at the third hour Examination of the urine by polarimeter showed dextrorotation and agreed with the results obtained by Benedict's method A fermentation test with yeast gave positive results, showing that the reducing substance in urine is glucose, not pentose After the ingestion of 100 gm levulose, the urine showed sugar after 30 minutes and continuing for 3 hours, with a total excretion of 0.09 gm The polarimeter showed left rotation, blood sugar, a maximum of 0.143 per cent, with return to normal in the second hour

Summary—After the ingestion of more than 34 gm starch, the urine showed sugar without any hyperglycemia, after 100 gm starch the urine contained 0.25 gm sugar, while after 200 gm starch the urine showed only 0.17 gm sugar, the maximum of blood sugar was 0.115 per cent after ingestion of 100 gm starch and 0.145 per cent

TABLE 2—DETERMINATION OF CARBOHYDRATE TOLERANCE—

Date, 1917	Diet (Test meals at 9 a m after fasting over night)							Urine			
	Foodstuffs, Gm					Carbo- hydrate, Gm	Fat, Gm	Volume, C c			
	Bread	Butter	Coffee	Cream	Salt			1 Hr	2 Hrs	3 Hrs	4 Hrs
Nov 29	45	30	2 cups			27	25	53	40	24	31
Nov 30	55	30	2 cups		1	33	25	45	39	21	20
Dec 1	65	30	2 cups		1	39	25	46	28	25	30
Dec 2	Banana 150		2 cups			33		44	40	23	28
Dec 3	Oatmeal 50	30	2 cups	30	1	34	31	50	33	40	30
Dec 4	Potato 150	30	2 cups	30	1	36	31	51	42	36	21

* Sugar test by Benedict's method, shows very slight reduction, qualitatively not measurable

TABLE 3—STARCH TEST TEST MEALS—

Date, 1917	Diet (Test meals at 9 a m after fasting over night)							Urine									
	Foodstuffs, Gm					Carbo- hydrate, Gm	Fat, Gm	Volume, C c Dextrose									
		But- ter	Cof- fee	Cream	Salt			30 Min	1 Hr	1 1/2 Hr	2 Hrs	2 1/2 Hrs	3 Hrs	3 1/2 Hrs	4 Hrs	4 1/2 Hrs	
Dec 5	Rice, 130 gm (dry weight), boiled with 100 gm water	30	2 cups	30	4	100	31		42 +		27 +		23 +		20 +	16 —	
Dec 14	Starch (Merck), 200 gm Paste made with 100 gm water		2 cups			200		45 +	8 +	15 +	6 ±	9 +	11 —	10 —	8 —	7 —	

TABLE 4—SUGAR TEST SUGAR AT—

Date, 1917	Glu- cose, Gm	Water, C c	Urine										Sugar in Hours, Per Cent Total Quantities Sugar, Gm			
			Volume, C c Dextrose													
			30 Min	1 Hr	1 1/2 Hrs	2 Hrs	2 1/2 Hrs	3 Hrs	3 1/2 Hrs	4 Hrs	4 1/2 Hrs		1 Hr	2 Hrs	3 Hrs	4 Hrs
Dec 19	50	300	30 +	15 +	16 ±	30 —	32 —	—	—	—	—		0 14 0 063			
Nov 1	100	500	182 +	100 +	42 +	76 —	50 —	—	—	—	—		0 32 0 68	0 16 0 16		
Dec 26	200	300	11 +	8 +		17 +	6 +	6 +	5 +	4 +	8 ±		1 26 0 24	1 08 0 19	0 99 0 12	0 39 0 04
Dec 8	Levu- lose 100	300	35 +	12 +	4 +	11 +	6 +	21 +	23 —							

MEALS AT 9 A M, AFTER FASTING OVER NIGHT

Urine			Blood								Remarks
Dextrose			Sugar in Whole Blood, Per Cent								
2 Hrs	3 Hrs	4 Hrs	Before Test	30 Min	1 Hr	1 5 Hrs	2 Hrs	2 5 Hrs	3 Hrs	3 5 Hrs	
—	—	—									
Trace*	—	—	0 081	0 085	0 087	0 082	0 085	0 086		0 071	
Trace	—	—				0 071					Sugar in plasma in 1 5 hr, 0 102 per cent
Trace	—	—				0 081					

A M AFTER FASTING OVER NIGHT

Urine				Blood									
Hours, Per Cent antities Sugar, Gm			Excreted Sugar in Toto	Sugar in Whole Blood, Per Cent Sugar in Plasma, Per Cent									
2 Hrs	3 Hrs	4 Hrs		Before Test	30 Min	1 Hr	1 5 Hrs	2 Hrs	2 5 Hrs	3 Hrs	3 5 Hrs	4 Hrs	5 Hrs
0 26 0 07	0 29 0 067	0 18 0 04	= 0 25 gm Polarimetric 0 19 per cent	0 076 0 108		0 069 0 115		0 058 0 111		0 057 0 083			0 035 0 085
0 3 0 06				0 08 0 105	0 122 0 139		0 105 0 133		0 118 0 145		0 093 0 102		

M, AFTER FASTING OVER NIGHT

Total Sugar Excreted	Blood								
	Sugar in Whole Blood, Per Cent Sugar in Plasma, Per Cent								
	Before Test	30 Min	1 Hr	1 5 Hrs	2 Hrs	2 5 Hrs	3 Hrs	3 5 Hrs	4 Hrs
gm	0 082 0 097	0 085 0 128	0 097 0 116		0 088 0 094				
m	Plasma 0 09	0 164	0 135	0 123	0 131		0 095		
m per cent in toto imetric 0 83 per	0 081 0 091	0 112 0 175	0 099 0 133		0 098 0 121		0 082 0 105		0 097 0 133
r cent imetric left ro a 0 098 per cent	0 072 0 101	0 071 0 143	0 061 0 128		0 094 0 106		0 061 0 114		

after 200 gm starch. Furthermore, after the ingestion of 100 gm glucose, more sugar was excreted in the urine than when 200 gm were taken, while the blood sugar was higher and remained higher for a longer period after 200 gm glucose was ingested than after 100 gm. When levulose was given it was excreted as levulose itself, not as glucose.

The Renal Threshold for Glucose—There are many reports concerning the renal threshold for glucose of the normal person. It is generally accepted that the kidney is permeable for sugar when the blood sugar reaches 0.16 to 0.17 per cent. Hamman and Hirschman¹⁹ say that in a normal individual the renal threshold is not a constant factor, but is usually between 0.17 and 0.18 per cent of blood sugar although some otherwise normal individuals have a low renal threshold, below 0.14 per cent (0.12 to 0.14 per cent, or 0.13 to 0.14 per cent). Foster²⁰ found the renal threshold between 0.149 and 0.164 per cent in a patient who had undergone ether narcosis. Jacobsen²¹ gives the blood concentration as 0.16 to 0.17 per cent. In the person reported on here, the renal threshold is as follows: whole blood, 0.069 to 0.071 to 0.081 to 0.085 per cent, plasma, 0.115 per cent.

Hyperglycemia After the Intake of Carbohydrate and Glucose—Much has been written on this subject, but very little that is trustworthy. For this the apparent reason is that prior to the introduction of Bang's method in 1914 and the present more accurate method of Lewis and Benedict a determination involved the use of much more blood than is now required, with consequently but one or two tests in each case, whereas an examination is requisite every thirty minutes. Consequently the conclusions drawn from former experiments involve confusion.

Frank,²² in 1911 asserted that in eight persons hyperglycemia of from 0.12 to 0.18 per cent was found in the blood plasma after the intake of 100 gm glucose in one hour's time, and that three persons showed a little sugar in the urine. Tachau²³ (1911), reported that no hyperglycemia was seen in one hour's time after a dose of 100 gm sugar. Bing and B. Jakobsen²⁴ (Bang's micromethod) found hyperglycemia of 0.098 to 0.17 per cent. Among ten persons, after intake of glucose, two showed 50 per cent and one showed 70 per cent rise of blood sugar. The average rise after one hour was 36 per cent,

19 Hamman, L., and Hirschman, I. I. Studies on Blood Sugar, *THE ARCHIVES INT. MED.*, 1917, **20**, 761.

20 Foster. *Am. Soc. Adv. Chem. Invest.*, 1917. Cited by Joslin (Footnote 4).

21 Jacobsen, Th. B. Untersuchungen über den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, Zuckerkranken u. graviden Personen, *Biochem. Ztschr.*, 1913, **56**, 471.

22 Frank, E. Weitere Beiträge zur Physiologie des Blutzuckers, *Ztschr. f. physiol. Chem.*, 1911, **70**, 291.

23 Tachau, H. Ueber alimentäre Hyperglykämie, *Deutsch. Arch. f. klin. Med.*, 1911, **104**, 432.

24 Bing, H. J., and Jakobsen, B. Blutuntersuchungen unter normalen u. einiger pathologischen Verhältnissen, *Deutsch. Arch. f. klin. Med.*, 1914, **113**, 571.

and after two hours only 11 per cent. These authors believe that a rise of more than 50 per cent at the end of the first hour must be considered as pathologic.

Th. B. Jacobsen²¹ (Bang's micromethod) found that 100 gm glucose produces a rapid hyperglycemia which usually reaches its maximum in from fifteen to thirty minutes after the intake, keeps up one to three hours, and then falls to normal or even below. His experiments included fourteen persons whom he held to be normal. Among them six persons showed no urinary sugar, with blood sugar reaching from 0.12 to 0.16 per cent. Another group of eight persons showed sugar in the urine, with blood sugar of 0.17 to 0.227 per cent. However, the greatest amount excreted was only 1.38 gm. In the first group of six persons showing sugar, the hyperglycemia lasted about 1.75 hours, in the second group, about 2.5 hours. After 167 gm bread (100 gm carbohydrate), all fourteen persons reacted with a hyperglycemia (0.138 to 0.206 per cent) which lasted from two to four hours, and six cases showed glycosuria (0.06 to 0.92 gm). The only difference between the effect of dextrose and of starch was in the rapidity of the rise and fall of the blood sugar curve, that is, only a quantitative difference due to the difference in the rate of absorption. Jacobsen's results seem to be somewhat higher than normal, according to our present conception. There is a possibility that the use of the method was not accurate, with consequent high results, or that the experiments included persons of carbohydrate tolerance lower than normal.

Hopkins²⁵ (Bang's micromethod), in experiments with eight persons, found that the blood sugar reached its maximum (0.14 to 0.156 per cent) in 30 minutes and lasted 2 hours. No urine examinations are reported. Graham²⁶ (Bang's micromethod), with three persons, noted that after 100 gm glucose, the greatest rise of blood sugar was from 0.09 to 0.18 per cent, and the smallest was from 0.095 to 0.14 per cent. The maximum was usually reached in 20 minutes with return to the original level in from 1 to 1.5 hours. Cummings and Piness,²⁷ after the intake of 100 gm glucose, found about a 50 per cent rise during the first hour, with a drop of about one half of this during the second hour. In subjects having a low tolerance for sugar, the rise following the ingestion of 100 gm glucose is distinctly higher than normal and the high level is well sustained up to the end of the second hour.

Hamman and Hirschman¹⁹ (Lewis and Benedict's method) say that in the normal person, after the ingestion of 100 gm glucose the blood sugar rises promptly to a level not exceeding 0.15 per cent, the high point is usually reached in about 30 minutes, and the whole reaction lasts from 1 to 2 hours, occasionally longer. They noted in many instances that where there is a considerable glycosuria, the excretion of sugar continues long after the blood sugar has fallen below the level at which it first appeared.

This latter fact—the continued excretion of sugar after the fall of blood sugar—may also be remarked in my case. Here, the maximum

25 Hopkins, A. R. Studies in the Concentration of Blood Sugar in Health and Disease as Determined by Bang's Micromethod, *Am Jour Med Sc*, 1915, **149**, 254.

26 Graham, G. Variations in the Blood Sugar in Health, *Jour Physiol*, 1915-1916, **1**, 285.

27 Cummings, R., and Piness, G. A Study of Blood Sugar. Comparison of Tolerance for Glucose in Diabetic and Normal Subjects, *THE ARCHIVES INT MED*, 1917, **19**, 777.

height and duration of the hyperglycemia after starch and glucose remain within the normal limit, the excreted sugar is below 1 gm, and there is no proportion between the glucose intake and the excreted sugar. Therefore, it is difficult to consider this case as a diabetes mellitus, but there is almost no doubt that it is a renal glycosuria, since the sugar excretion is due to the abnormally lowered threshold of the kidney, not to a pathologic hyperglycemia.

The Blood Sugar and the Renal Threshold of Diabetes—The blood sugar of the diabetic is in higher concentration than normal. It is only in the mild form of the disease or under strict treatment that the blood sugar is normal. Following the administration of 100 gm of glucose the rise in the blood sugar is greater than normal, and the rise is sustained longer than in normal men. Jacobsen²¹ found in two cases of diabetes that an appreciable amount of sugar appeared in the urine, with sugar-freedom at the beginning of the experiment, and blood sugar below 0.15 per cent. He explained these facts on the ground that the diabetic excretes more sugar than normal at a certain level of blood sugar. It is also known that there is frequently a higher threshold for sugar in diabetics without evident renal lesions, some are free from glycosuria even when the blood sugar reaches 0.5 per cent.

According to Cummings and Piness,²⁷ in the mild form of diabetes, following the administration of 100 gm glucose, the rise of blood sugar is longer sustained than normal, even to the end of the second hour. In a really or moderately severe case the blood sugar is higher two hours after intake of 100 gm glucose than one hour after. Hamman and Hirschman¹⁹ confirmed the finding that the hyperglycemia in mild diabetes is abnormal in definite respects: the blood sugar rose more slowly and reached its highest point later than normal, it also rose to a much higher level, all their three cases exceeding 0.2 per cent. Likewise, the fall of the blood sugar occurred much more slowly than in the normal, the whole reaction occupying from three to four hours. These authors believe that the *duration* of the hyperglycemia is a more important index of the severity of the alteration of carbohydrate metabolism than is the height of the hyperglycemia. Concerning the renal threshold in diabetes, they found that mild cases show a normal level while moderately severe cases sometimes show a threshold below 0.15 per cent, but usually higher.

Graham,²⁸ in 1916, reported lower and higher thresholds for diabetes. His patient of lower threshold—a man of 32—in whom glycosuria had been detected five years previously, followed an unrestricted diet most of the time, with a sugar output of about 10 to 30 gm daily. The blood sugar before a meal and

28. Graham, G. Variations in the "Leak Point" in Diabetes Mellitus. I. A Low Level, *Jour Physiol*, 1915, **49**, *Proc Physiol Soc*, p. 47.

after semi-starvation for twenty-four hours varied from 0.1 to 0.13 per cent, and sugar was always present in the urine. After 100 gm dextrose the blood sugar rose 0.22 per cent in one hour and had not quite fallen to its original level three hours later. The results in this case seem to indicate that the escape of sugar was due in some degree to permeability of the kidneys, or in other words, this case might represent a combination of renal glycosuria and true diabetes.

The Test of the Renal Function—As it was clear that my case showed a lowered threshold for sugar, examinations of the renal function were made. McLean's²⁹ adaptation of the Ambard constant was employed for the determination of the excretion of urea and sodium chlorid.

TABLE 5—THE RELATION OF THE RATE OF UREA EXCRETION TO CONCENTRATION IN THE BLOOD

Dec 21, 1917 (10 20 a m to 11 32 a m), bleeding at 10 50, total urine, 168 c c

Weight, Kg	Urea				NH ₃	Acidity (Fohn)
	Per Liter of Blood, Gm	Per Liter of Urine, Gm	Per 24 Hours, Gm	Index	Per Liter of Urine, Gm	N — Acid per Liter 10 of Urine C c
51	0.244	9.05	30.41	270	0.229	55.8

Breakfast at 8 a m, bread, 40 gm, butter, 20 gm, 2 eggs, half grape fruit, 1 cup of tea

TABLE 6—THE RELATION OF THE RATE OF CHLORID EXCRETION (CALCULATED AS SODIUM CHLORID) TO CONCENTRATION IN PLASMA

Same morning

Weight, Kg	Sodium Chlorid					
	Per Liter of Urine, Gm	Per 24 Hours, Gm	Per Liter of Plasma			Threshold
			Calculated, Gm	Actual, Gm	Difference, Gm	
51	7.8	26.2	6.21	6.25	+0.04	5.66

McLean has shown that the urea excretion index as an indicator of renal function is preferable to determinations of blood urea interpreted without reference to urea excretion. The tests were conducted as follows: breakfast at 8 a m, at 9 50, 200 gm water drunk, at 10 20, urine passed, at 10 50, blood taken, at 11 32, that is, seventy-two minutes after the bladder was first emptied, the urine was collected, measured, and used for analysis. McLean's tables show that the normal concentration of urea in the blood varies from 0.2 to 0.5 gm per liter. The normal urea index lies above 80, with an average of 120, based on 100 tests. Any index below 80 is considered abnormal, and the degree of impairment of functional ability or damage to the kidneys becomes greater as the index gets lower. An index above 300 may occur in healthy young persons with low blood urea, it may result from the washing out of urea with a high fluid output, or it may occur with "vascular hypersensitiveness" (Schlayer).

²⁹ McLean, F C. The Numerical Laws Governing the Rate of Excretion of Urea and Chlorids in Man, Jour Exper Med, 1915, **22**, Nos 2 and 3, pp 212 and 366.

The urea index of my case is 270 This is due to the high fluid output, the rate of water excretion for twenty-four hours being 3,300 c c by calculation, while the daily volume of urine is always from 1,200 to 1,800 c c actually

McLean has confirmed Ambard and Weill as to the law of chlorid excretion in relation to its blood concentration, and has found that normally the plasma chlorid varies from 5.62 to 6.25 gm per liter according to the amount of salt ingested There is a close agreement between the chlorid calculated in the plasma by Ambard and Weill's constant and that actually found

The actual plasma sodium chlorid content in my case is 6.25, and the difference between the actual content and the calculated result is 0.04 Consequently, in this case the renal test shows no disturbance of kidney function according to the urea and chlorid excretion

The Relation Between Diabetes and Nephritis—It is well known clinically that when chronic nephritis occurs as a complication in diabetes, the kidney excretes less sugar than before and the sugar content in the urine is diminished It is also known that hyperglycemia (without glycosuria) often occurs in cases of nephritis

Myers and Bailey³⁰ lately reported hyperglycemia in nephritis and discussed the elevating influence of the nephritis generally accompanying advanced diabetes on the threshold of sugar excretion According to Hopkins,²⁵ nephritic cases all furnish very high figures of blood sugar after feeding glucose, the duration of hyperglycemia lying between that of normal and of diabetic patients Bing and B. Jacobsen,²⁴ in some cases of nephritis, after ingestion of glucose found an abnormal hyperglycemia but no alimentary glycosuria Hamman and Hirschman¹⁹ say that the renal threshold in nephritis is often above 0.2 per cent In spite of the fact of the frequently high renal threshold in nephritis, however, there is sometimes a normal threshold in nephritis, and these authors found also a nephritis with a low threshold for glucose, in the neighborhood of 0.15 per cent

As regards the kidney function in diabetes, Fitz³¹ found that the urea index in the majority of the cases tended to be normal or abnormally high In diabetes the plasma chlorid is usually lower than would be calculated from the chlorid excretion according to the formula of Ambard and Weill McLean²⁹ found a lowering of the plasma chlorid in the majority of his observations in twenty-four cases of diabetes

³⁰ Myers, V. C., and Bailey, C. V. The Lewis and Benedict Methods for the Estimation of Blood Sugar, with Some Observations Obtained in Disease, *Jour Biol Chem*, 1916, **24**, 147

³¹ Fitz, R. Observations on Kidney Function in Diabetes Mellitus, *THE ARCHIVES INT MED*, 1917, **20**, 809

REVIEW OF THE HITHERTO REPORTED CASES OF RENAL GLYCOSURIA

A search of the literature of renal glycosuria gives the following data

1 Klemperer¹ (1896, Congress of Internal Medicine, Berlin) reported a case of old nephritis which showed 0.35 per cent sugar in the urine with the normal figure for blood sugar, the intake of bread and 150 gm glucose exerted no influence on the sugar content either of urine or blood, sugar in the whole blood was 0.175 per cent, which, according to our modern conception, must be considered as hyperglycemia. At the Congress of Internal Medicine in Wiesbaden in 1913, where the problem of renal glycosuria was again discussed, Klemperer's case was no longer recognized as a renal glycosuria.

2 Luthje² reported a patient, aged 22, a merchant, with gonorrhea, cystitis, and probably ascending pyelonephritis. In the urine were found albumin and sugar below 1 per cent, reaching at the utmost 15 gm a day. There was a constant excretion of sugar showing but very slight variation in the quantity despite great difference of carbohydrate intake per day. The single determination of sugar in the blood showed sugar as 0.055 per cent in the whole blood. No mention was made, however, of the time or the relation to the diet, so that a conclusion concerning this case is consequently impossible. Luthje claimed a relation between glycosuria and the nephritis because his case was apparently free from sugar *before* the nephritis, while sugar appeared in the urine shortly *after* the nephritis.

3 Bonmger³ describes a patient, a man, aged 37, an alcoholic, who said that he had once shown urinary sugar of 2 per cent. After admission to the hospital he excreted sugar to the extent 0.2 per cent on normal diet. During thirty-three days' observation in hospital, the percentage of sugar in the urine was remarkably constant in spite of great differences in carbohydrate intake, varying only between 0.1 and 0.5 per cent. The sugar content of the serum was 0.097 per cent, of whole blood, 0.078 per cent. Occasionally when the urine contained 0.5 per cent sugar, the blood sugar was 0.062 per cent. This patient, who was observed for six years, is in perfect health and still excretes a small amount of sugar. His son is also affected with renal glycosuria.

4 Weiland⁴ makes a report of three cases which are not all, however, renal glycosuria.

5 Tachau⁵ reports a patient, 21 years of age, a merchant, who developed gastro-enteritis after an excessive indulgence in fruit. The urine showed albumin, erythrocytes and casts (transient acute nephritis). The following schedule shows the results of experiments.

Diet	Days Observed	Urinary Glucose in 24 Hours, Gm
Carbohydrate-free	4	0
Mixed (158 to 192 gm C H)	6	0
Mixed (124 to 412 gm C H)	15	1.1 to 6.0
Mixed plus 100 gm dextrose	3	0.6 to 4.2

The percentage of sugar in the whole blood after fasting was from 0.085 to 0.086, one hour after 100 gm glucose it was 0.07 to 0.109.

5 E Frank⁶ reports two cases. (a) a patient aged 51, who for four years had suffered from severe diarrhea of four weeks' duration, four or five times a year, without apparent cause. After the attacks glycosuria lasting about ten days was observed. Dextrose in the urine ranged from 0.05 to 0.5 per

cent, sugar in the whole blood equaled 0.09 per cent, in the plasma, 0.106 per cent, (b) this patient suffered from a nervous complaint. Sugar in the urine was from 0.4 to 0.65 per cent, in the whole blood, 0.08 per cent, in the plasma, 0.08 per cent. In both cases, however, the time of the blood sugar determination and its relation to the diet were not shown, consequently, this report is incomplete. Frank's paper is valuable rather as a report of the literature and of his own experiments of renal glycosuria in animals under heavy-metal intoxication, as mercury, uranium and chrome. In these experiments he proved a true renal glycosuria. His exposition of increased renal permeability after poisoning with heavy metals, and also during pregnancy, suggests the existence of a clinically permanent renal glycosuria. Frank further emphasized the importance of estimating sugar in the plasma instead of in the whole blood.

7 In de Langen's¹⁰ case, a patient of 22 years, sugar was always present in the urine, the quantity of excreted sugar varying between 4 and 19 gm in twenty-four hours, and showing no proportional relations to the quantity of carbohydrate intake. After a carbohydrate-free diet there was a high content of sugar in the urine, while the smallest excretion of sugar was seen after a high carbohydrate intake. Intake of theobromin sodium salicylate (diuretin), which, according to some authors, influences sugar excretion, had no influence in this case. Blood sugar was determined in whole blood by Bang's method, there was hypoglycemia (0.054 to 0.073 per cent), these results are, however, not decisive because the determination was not made until three hours after the meals instead of one or two hours, but they probably serve to rule out diabetes.

8 Galambos¹¹ reported a patient 50 years of age. During observation over a period of twenty-one days, while the carbohydrate content of the diet was between 50 and 354 gm per day, the glycosuria varied between 66 and 198 gm and the concentration of urinary dextrose between 2.6 and 7.4 per cent. Blood sugar during fasting showed 0.089 and 0.052 per cent, one and a half hours after taking 100 gm dextrose it was 0.17 per cent. After caffeine, the urinary sugar was increased with the increase of urine volume. This case shows polyuria, polydipsia and acidosis, with much urinary sugar. The respiratory quotient was said to be 0.709 in fasting.

9 Lewis and Mosenthal¹² report the case of a man aged 29, who for the previous two or three years had had a tendency to increased frequency of urination during the day, but not at night. This condition had evidently been a pollakiuria rather than a polyuria, as the quantities voided apparently had not exceeded the normal. There were no diabetic symptoms. The patient excreted from 11 to 13 gm sugar in twenty-four hours on "ward light diet." After the ingestion of 100 gm glucose a hyperglycemia of 0.15 per cent was evident within thirty-five minutes. Two hours and five minutes after the experiment was begun the blood sugar level returned to normal and subsequently became depressed below the normal level. The phenolsulphonephthalein test showed an excretion of 42 per cent in two hours. Ambard's constant, determined at various times, was from 0.07 to 0.11 per cent. The kidneys were intact as far as physical and urinary signs were concerned, functional tests, however, revealed some impairment, as shown by a slightly diminished phenolsulphonephthalein excretion and an Ambard's constant barely within the upper normal figure.

10 Murlin and Niles¹³ report a case of a man aged 20, with no diabetic heredity, who two years previously had furuncles, polyuria and thirst with loss of 10 pounds in one month. After admission to the hospital, sugar in the urine was between 19 and 34 gm when the carbohydrate in the diet was between 15 and 100 gm. Examination for blood sugar at 11 a. m., five hours after break-

fast, revealed a normal percentage on several days. As this case was accompanied by diabetic symptoms, however, and as the blood sugar was not tested at the proper time, it is hard to classify it as renal glycosuria.

11 Strouse¹⁴ had a patient aged 13 who felt perfectly well. With noncarbohydrate diet the urine showed a trace of sugar, not quantitatively measurable. After prolonged ingestion of carbohydrate, the urine showed the same trace of sugar, apparently no more and no less than was present when the patient was on a carbohydrate-free diet. Blood sugar was 0.04 per cent one hour after a meal rich in carbohydrate.

DISCUSSION

There has been a gradual change from the former to our present conception of renal glycosuria. Klemperer¹ regarded this condition as a sort of anomaly of metabolism characterized by normal content of blood sugar with independence of sugar excretion from carbohydrate intake. Luthje⁵ and Naunyn³² believed that a relation existed between renal glycosuria and nephritis. Naunyn³² remarked a renal glycosuria occurring with granular nephritis; he reported three cases, but the lack of blood sugar determination leaves us uncertain whether there was hyperglycemia or hypoglycemia. Naunyn believes that nephritis influences the epithelia of the kidney to facilitate the excretion of sugar. This same author also reported glycosuria occurring after renal hemorrhage which had no apparent relation to the diet and which disappeared without any restriction of diet.

It is believed that glycosuria in pregnancy and in the puerperium is probably a renal process. Furthermore, Frank's⁹ experiments confirm the work of many investigators concerning experimental renal glycosuria due to an increased permeability for sugar after poisoning with mercury, uranium, and chromate. Among the clinical cases of renal glycosuria already cited, the ones showing a previous affection of the kidney are those of Klemperer, Luthje and Tachau. My patient also has a record of febrile albuminuria during typhoid fever ten years previously. But the general conception now is that the existence of kidney affection, that is, anatomic change of the kidney (morbus brighti and contracted kidney) is not necessary for the occurrence of renal glycosuria. The reasons for the permeability of the kidney to sugar are not yet known.

It has been shown that the blood sugar rises after meals (Bing and B. Jakobsen,²⁴ Th. B. Jakobsen,²¹ Strouse³³), and Joslin⁴ says that the percentage of sugar in the blood of normal individuals rises promptly after meals and may reach 0.17 per cent. Accordingly, if the sugar threshold of the kidney is below the normal level, 0.17 to 0.18 per cent,

32 Naunyn, B. *Der Diabetes mellitus*, Wien, 1906, p. 136.

33 Strouse, S., Stein, I. F., and Wiseley, A. *The Accurate Clinical Study of Blood Sugar*, Bull. Johns Hopkins Hosp., 1915, 26, 211.

there must occur regularly after meals a glycosuria which lasts for a certain time and disappears spontaneously. It is pointed out by Hamman and Hirschman¹⁹ that the lowered renal threshold may occur in otherwise normal individuals. They believe that a relation between the lowered renal threshold and renal glycosuria is obvious.

The intensity of the renal glycosuria will vary with the degree of the affection of the kidney, that is, its permeability to dextrose. (1) If the permeability is severely affected, with marked depression, urinary sugar will constantly appear even when the blood sugar content is very low. (2) When the renal permeability is but mildly affected, sugar will appear only at the high level of hyperglycemia of physiologic limit, and there will be no sugar in the urine with carbohydrate-free diet, because with that diet there occurs no high physiologic hyperglycemia. Under a diet rich in carbohydrate, the blood sugar will rise to the high level of physiologic hyperglycemia and sugar will appear in the urine. This high level of physiologic hyperglycemia is, in the normal subject with normal permeability of the kidney, a preglycosuric level.

Since we know that the blood sugar undergoes marked and rapid fluctuation after the ingestion of carbohydrate, and that urinary sugar has some relationship to hyperglycemia after meals, it is hardly possible to deny, to a certain extent, at least, the existence of a relationship of urinary sugar in renal glycosuria to the carbohydrate content of the diet. In the case under consideration there was no urinary sugar when the carbohydrate in the diet was below 34 gm, because the alimentary hyperglycemia occurring with that diet is under the threshold of the kidney for sugar. Blood sugar was highest after 200 gm glucose, but the urinary glucose in that case was less than after 100 gm glucose.

From the foregoing facts it is apparent that renal glycosuria may depend to a certain extent on the carbohydrate content of the diet. Therefore, a classification of this condition is necessary. (1) When the renal permeability is but slightly affected, glycosuria may not appear after a carbohydrate-poor diet, but, when it is severely affected, glycosuria will not disappear even after the entire withholding of carbohydrate from the diet. (2) Urinary sugar is not excreted proportionately to the increase and decrease of carbohydrate in the diet.

Von Noorden² remarks that in mild diabetes the urinary sugar is often independent of the carbohydrate intake. Therefore, too much attention must not be paid to the fact of the independence of urinary sugar to the carbohydrate in the diet.

The most important factor in the diagnosis of renal glycosuria is the presence of the normal level of the blood sugar when sugar appears in the urine.

Von Noorden² also says that renal glycosuria must be observed not a few weeks or months, but over a long period of time, since its progress is different from that of ordinary diabetes. Joslin⁴ remarks the same thing. The author's case has been observed for five years, and the tolerance for carbohydrate is still the same and the subject is in good health.

Suggestions as to the Nature of Renal Glycosuria—In the foregoing discussion I have tried to show that renal glycosuria may be defined according to the following characteristics:

1 Glycosuria occurs without *abnormal* hyperglycemia. Abnormal hyperglycemia, as previously stated, is entirely different from alimentary hyperglycemia of from 0.16 to 0.17 per cent, which is physiologic. Glycosuria occurs although the blood sugar is within this physiologic limit.

2 There is no disturbance of carbohydrate metabolism, the nature of renal glycosuria is entirely different from that of true diabetes mellitus, and consequently, there are clinically no diabetic symptoms.

3 Urinary glucose may or may not have some relationship to the carbohydrate in the diet, according to the degree of permeability of the kidney. In a mild case, sugar will disappear from the urine during a carbohydrate-free diet, glucose usually appears after rich carbohydrate intake.

4 During a long period of time no progressive increase of the abnormality occurs.

It is obvious that the term "renal diabetes" is not fitting for the characteristics just described, since the condition is not diabetes, but is "alimentary renal glycosuria."

Diagnosis of Renal Glycosuria—Notwithstanding the fact that it is perfectly simple to observe that the lowering of the renal threshold results in the appearance of glucose in the urine without disturbance of intermediary carbohydrate metabolism, nevertheless, the question of renal glycosuria was left for a long time unsolved. The recent improved methods of blood sugar analysis have afforded the first opportunity of settling the question of blood sugar and especially of alimentary hyperglycemia. Now we know that when an individual shows sugar in the urine we must determine the blood sugar before we can make the diagnosis "diabetes," and furthermore, that in case of doubt, sugar must be determined in the plasma, because the renal threshold pertains most strictly to it. Examination of blood sugar is required not only once after fasting, but also at least twice every hour after a certain carbohydrate diet with resultant glycosuria. The elevation of the blood sugar and the renal threshold of the individual must

also be studied. Comparison of single blood sugar determinations is without value. By these means, just stated, we can learn whether the glycosuria is due to disturbance of carbohydrate metabolism or to the increased permeability of the kidney for sugar, according as the hyperglycemia present is within the physiologic limit or not. We learn at the same time the level of the renal threshold in the patient.

The glucose test, which must next be considered, consists in the study of the blood and urine of the patient beginning thirty minutes and continuing two or three hours following the intake of 100 gm glucose with from 250 to 300 gm water, after an over-night fast. This test shows the condition of carbohydrate assimilation of the individual. If the hyperglycemia still remains within the physiologic limit after the test, we may exclude diabetes mellitus and consider that the urinary sugar is due to the increased permeability of the kidney to sugar.

The one more important point is the observation of the case over a period of years, because, as remarked by von Noorden, there is a form of mild diabetes which shows a high tolerance for sugar in the early period of the disease. To differentiate renal glycosuria from this mild form of diabetes mellitus one must determine the course and watch the outcome.

Since renal glycosuria brings about no injury to the health or annoyance to the individual, it is possible that persons with a lowered sugar threshold may unconsciously for a long period excrete sugar in the urine after meals. The absence of symptoms may quite possibly conceal many cases of renal glycosuria which are not at present credited. It is also possible that some of the cases of the so-called mild diabetes in practice may belong to this form of glycosuria because the majority of them are diagnosed only by the examination of sugar in the urine, or, at most, by a single determination of blood sugar without relation to the preceding meal. An imperfect examination might easily diagnose as mild diabetes cases which in reality are renal glycosuria with a lowered threshold of the kidney for sugar and perfect carbohydrate metabolism.

Prognosis of Renal Glycosuria—The present conception of renal glycosuria is that this condition is stationary, the glycosuria has no tendency to increase and the subject remains in good health. My case shows, during five years, only the same slightly depressed threshold and consequently only intermittent glycosuria after a meal rich in carbohydrate. Whether this condition will continue for a long period of time, say 10 or 20 years, or whether sooner or later a marked depression with constant excretion of sugar in the urine will occur, only the future can reveal.

Therapy of Renal Glycosuria—It is believed at present that it is useless to keep to a strict diet in renal glycosuria. However, with the cases hitherto reported so few and the time of their observation so short there is no surety that it is harmless to give carbohydrate and glucose in large amounts to persons with lowered kidney thresholds since there is a chance that the depression might be thereby increased. The question is still open.

The author wishes to express his gratitude for the advice and criticism of Drs. F. M. Allen and D. D. Van Slyke throughout this work.

CONCERNING THE GASTRIC LESIONS OBSERVED IN EXPERIMENTAL BACTEREMIA *

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The frequency with which hemorrhage and erosions of the stomach mucosa are found in infections and intoxications has led some investigators to suggest the possibility of such conditions having a certain influence in the production of gastric ulcer. Although these lesions do at times simulate the so-called peptic ulcer, still there is considerable doubt as to whether they ever lead to the round or chronic gastric ulcer as it is observed in the human. It is almost impossible to say that any one factor acts as an exciting or contributing cause in the development of a gastric ulcer. The many theories which have been advanced illustrate the diversity of opinion, and we are today probably little more advanced in solving the problem than were the early writers. The ideas concerning the effect of an altered blood stream on the gastric mucosa, bringing about ulceration, as well as the part played by the central nervous system and local spasms of vessels themselves, are among several of the theories advanced by the early writers (Thorel¹). Virchow was of the opinion that thrombosis and embolism of some parts of the coronary system had to do with the production of ulcer, while Openchowsky and v Recklinghausen observed atheromatous lesions in the vessels of stomachs in which ulceration had occurred. According to Nauwerck² the alterations found in the blood vessels by the foregoing authors were secondary, as ulcers occurred in individuals in whom, he believed, infected food and an existing chronic gastritis were responsible for the condition. In this connection Ruzicka³ was of the opinion that the deleterious effect of the gastric juice on the mucosal cells is due to an alteration in the cells themselves and this author believed further that the superficial gastric cells are fairly easily injured by the gastric juice, while the deeper cells are more resistant to such insult. The mechanical theory was favored also by Stromeyer,⁴ and particularly the injurious effect caused by the friction of food on the gastric mucosa. Thus it

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1 Thorel Lubarsch Ostertag, 1898, 5, 142

2 Nauwerck Quoted by Thorel, Footnote 1

3 Ruzicka Wiener med Presse, 1897, 38, 10

4 Stromeyer Ziegler's Beitr, 1912, 54, 1

would appear that ulcerations are developed by a local digestion of the mucosa which as shown by Best⁵ are prevented under normal conditions by the presence of the antiferment in the cells

The occurrence of lesions in the stomach following infections and intoxications has been repeatedly observed, with the result that erosions and purpuric spots have been described in the stomach in a variety of conditions. Nauwerck observed ulcers of the stomach in

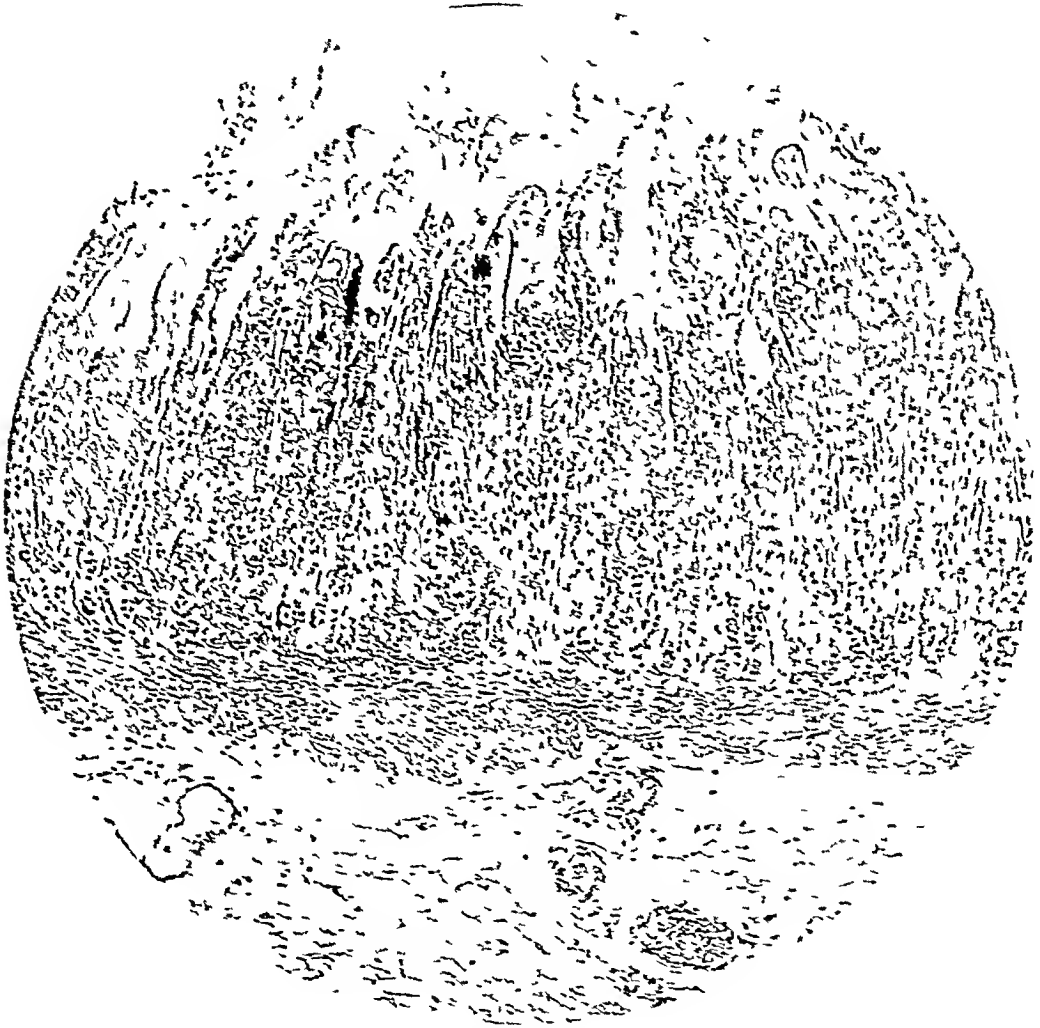


Fig 1—Stomach Rabbit 120 organism *S. salicarius* showing necrosis of folds with infiltration of polynuclear leukocytes and hemorrhage. There is extension of the inflammatory reaction into the muscularis mucosa.

scarlet fever, endocarditis and rheumatism and has described these lesions as round or streaky erosions, with necrosis of the mucosa not unlike those observed in multiple plugging of the capillaries by emboli. From this Nauwerck designated a particular kind of ulcer in rheumatism. Among other workers, Widal and Meslay⁶ also found ero-

⁵ Best, Verhandl. d. Deutsch. path. Gesellsch. 1913, 16, 385.

⁶ Widal and Meslay. Quoted by Thorel, Lubarsch, Ostertag, 1898, 5, 142.

sions in the gastric mucosa following wound erysipelas, while Schimlinsky⁷ described similar lesions in phlegmonous infection of the umbilical vein. In the so-called hemorrhagic infections, erosions and purpuric spots commonly occur in the stomach, and as Babes⁸ has recorded, it would appear that no single specific organism is responsible for hemorrhagic disease. Thus, any organism which has a damaging effect on the blood vessels causing molecular destruction

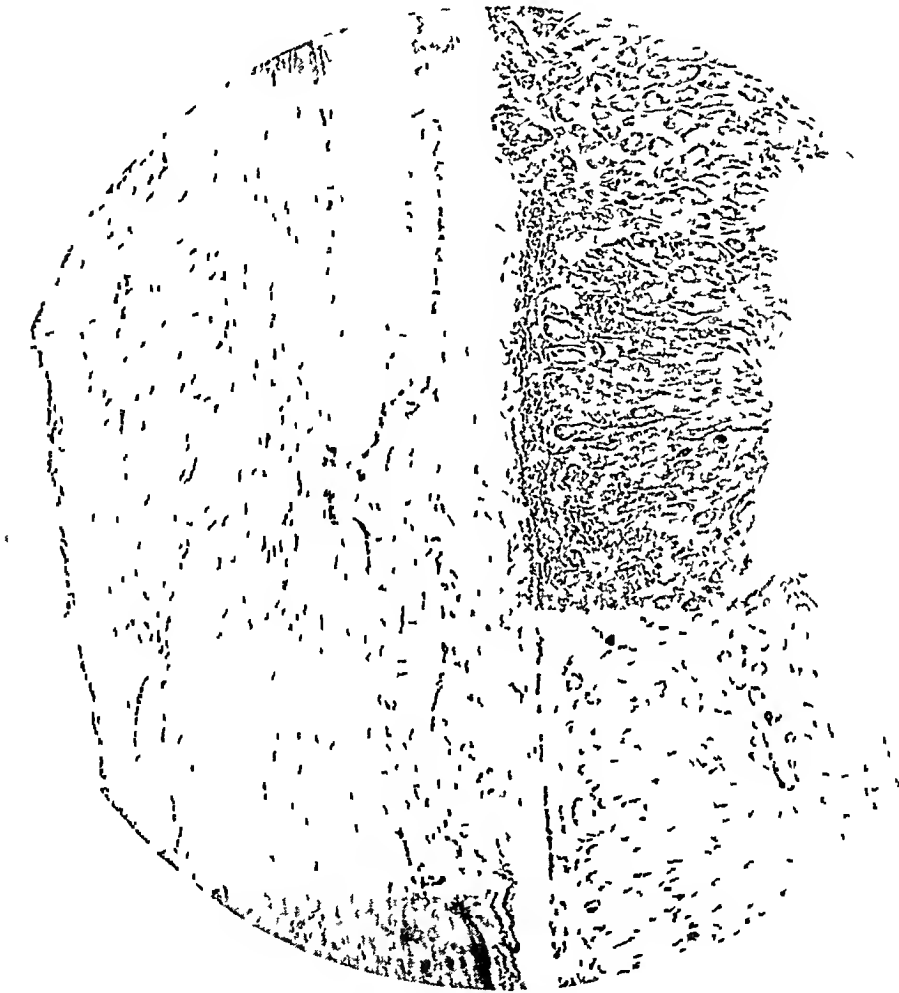


Fig 2—Stomach, Rabbit 113, organism, *S. subacidus*, showing hemorrhage, necrosis and infiltration of polynuclear leukocytes which extend slightly into the mucosa

of the walls may well be responsible for the disease. Likewise, the toxic products of bacteria are capable of producing not only purpuric conditions, but can also be the causal agent of excessive hemorrhages. Prominent among the authors who studied hemorrhagic disease was

7 Schimlinsky. Quoted by Thorel, Footnote 1

8 Babes. *Wien med Wchnschr*, 1892, **34**, 1321, **35**, 1356, **36**, 36 and 1394, *Idem Zentralbl f Bakt u Parasitenk*, 1891, **9**, 719

Howard,⁹ who described gastric and intestinal hemorrhage, in this condition, where capsulated gram-negative bacilli, streptococci and other organisms are directly concerned. This author concluded that hemorrhagic septicemia is, therefore, not to be regarded as a separate and distinct disease with definite and constant etiology, uniform anatomic lesions and clinical features, but rather as a toxemia attended

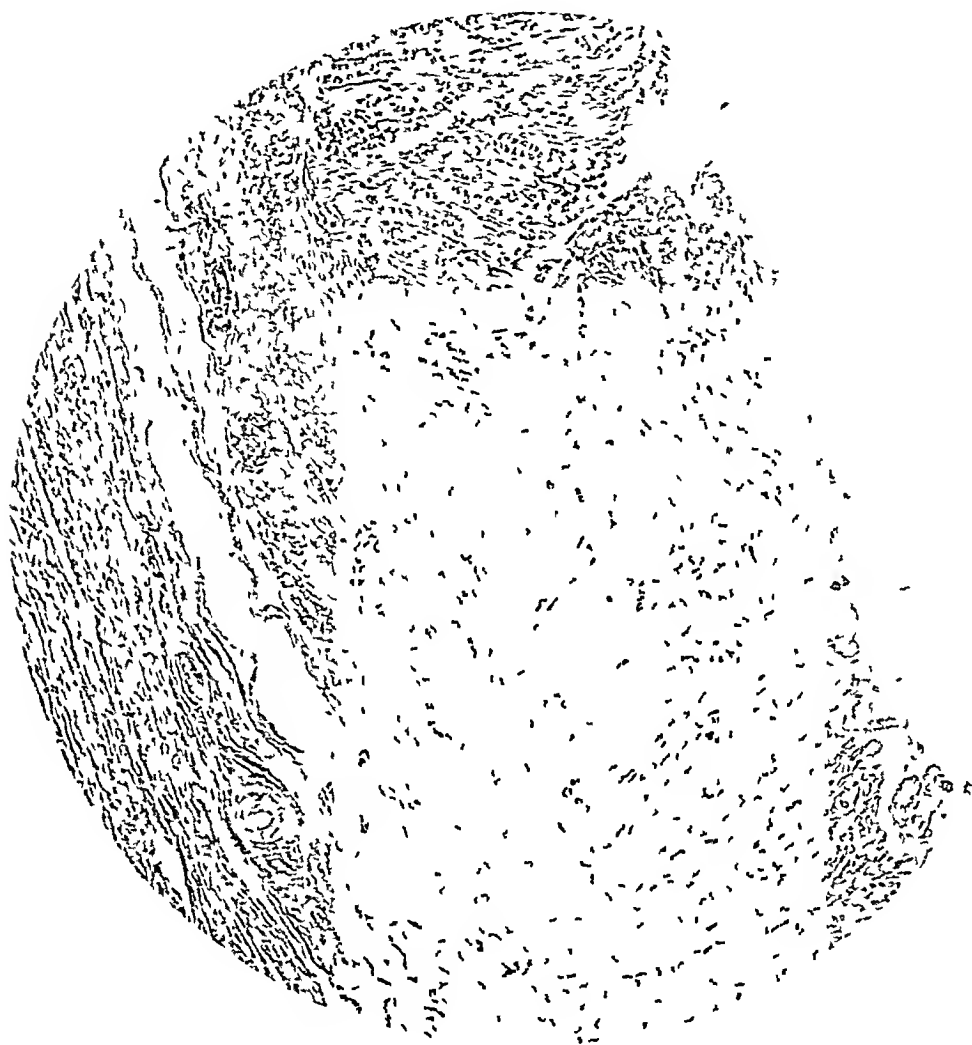


Fig 3 Stomach, Rabbit 135, organism, *S. pyogenes*, showing ulceration and necrosis of mucosa with hemorrhage and leukocytes scattered through the necrotic material. The infiltration of leukocytes extended to the outer border of the submucosa but not beyond it.

by such marked injury to the blood vessels and to the blood as to cause extreme dilation of the vessels and hemorrhages with various harmful effects on the body cells. Similar alterations were recorded by Claisse¹⁰ in pneumococcus septicemia.

⁹ Howard Jour Exper Med 1899 4, 149

¹⁰ Claisse Arch de med exper et d'anat path, 1891, 3, 379

Concerning ulcers of the stomach of this type, where it is maintained that the stomach is the only organ injured, Thorel made the very significant comment that ulcers due to infection are not found in otherwise sound people, but are seen in those persons suffering with a general infection. Oberndorfer¹¹ has described a type of hemorrhagic embolic enteritis which occurs in pyemia, while McCrae and

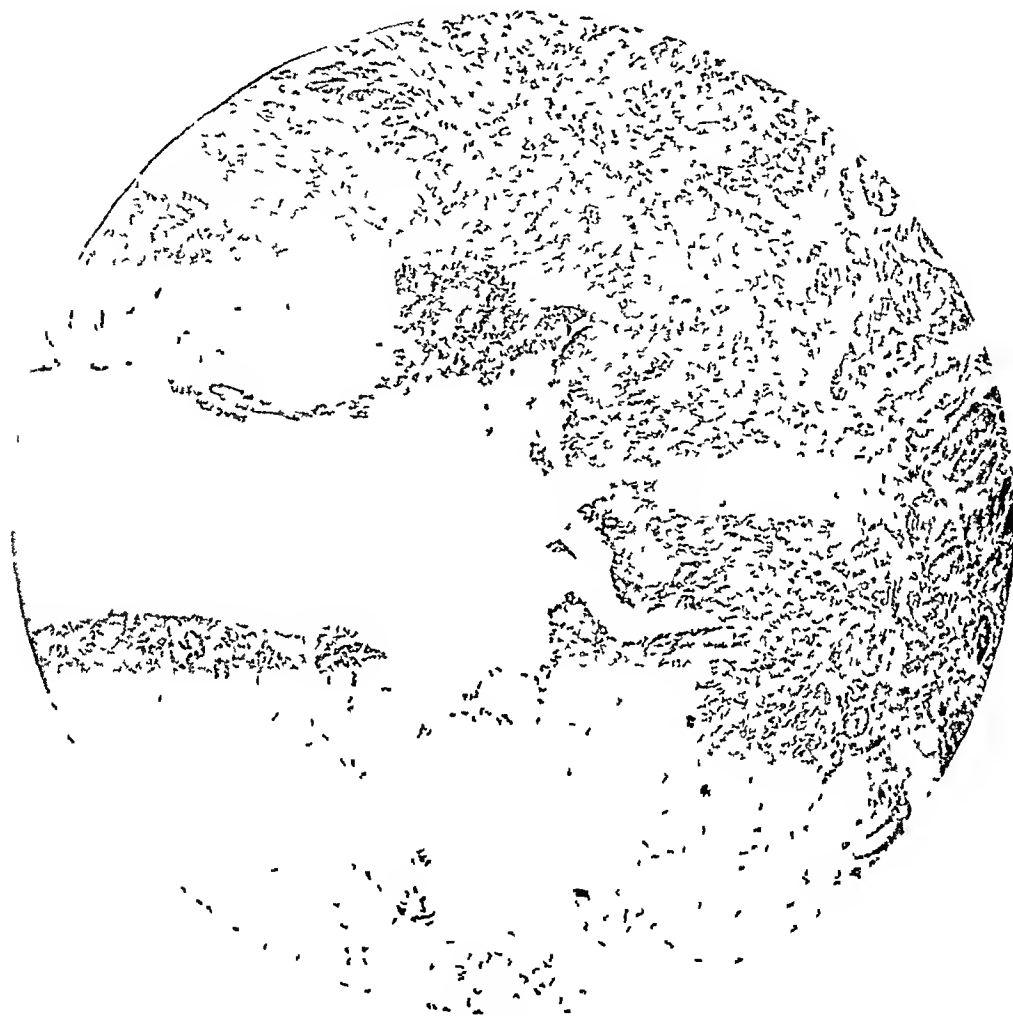


Fig 4—Stomach, Rabbit 69, spontaneous ulcer in pyloric ring

Bardeen¹² have collected a series of cases from the literature which showed duodenal ulcer following extensive burns

Just as gastric lesions have been found associated with a variety of conditions in human beings, so has it been the fortune of investigators to produce stomach lesions in experimental animals by diverse means. Bacteria have played their part in the work of several authors.

¹¹ Oberndorfer *Verhandl d deutsch path Gesellsch*, 1910, **14**, 159

¹² Bardeen *Johns Hopkins Hosp Rep*, 1898, **7**, 137

notably Stewart and West¹³ and Rosenow¹⁴ The first two workers succeeded in producing gastric erosions in five guinea-pigs which were injected intraperitoneally with a pathogenic strain of *B. Welchii* They were also able to produce similar lesions in guinea-pigs injected



Fig 5—Duodenum, Rabbit 55, organism, *B. acidilactici* and *Staphylococcus albus*, showing hemorrhage into mucosa with erosion of surface

with acetic acid In all instances these lesions were observed as erosions of the mucosa and submucosa with intact muscularis and serosa Among the more recent studies of the bacteriologic production of

13 Stewart and West Jour Immunol, 1916, **1**, 187

14 Rosenow Jour Infect Dis, 1915, **17**, 219, idem, Jour Am Med Asso, 1913, **61**, 1947

gastric ulcer is that of Rosenow, who found gastric ulcer in 60 per cent of animals injected with cultures of streptococci obtained from the tonsils of individuals suffering with gastric ulcer, while but 20 per cent of the animals injected with his so-called "indifferent" strains of streptococci developed gastric ulcer Ribbert¹⁵ was able to produce a more advanced type of lesion by freezing the stomach wall with ethyl chlorid After eight days, the muscularis showed marked erosion,



Fig 6—Duodenum, Rabbit 117, organism, *S equinus*, showing extensive hemorrhage into the mucosa and about the glands in the submucosa

with an exudate on the serosa and a cellular infiltration in the neighboring tissues An area 2 cm in diameter, representing the part frozen, was the only tissue affected It would appear also that several of the endocrinous glands may at times be associated with gastric alterations In this connection Mann¹⁶ found gastric erosions in

15 Ribbert Frank Ztschr f Path, 1915, 16, 343

16 Mann Jour Exper Med, 1916, 23, 203

adrenalectomized dogs and cats, while Finzi¹⁷ observed the same condition following partial adrenalectomy in dogs and rabbits. Following the subcutaneous and intravenous injection of epinephrin, Biedl¹⁸ noted inflammatory and degenerative changes in animals not only at the site of injection, but also in distant organs, such as the mucous membrane



Fig 7—Peyer's patch, Rabbit 70, organism, *B. acidus lactici*, showing hemorrhage into Peyer's patch with erosion of surface

and musculature of the stomach, intestines and urinary bladder. Similarly, Friedman¹⁹ described gastric ulcers following the injection of thyroid extract and adrenalectomy and later observed the development of duodenal ulcers after the injection of epinephrin. In reference to this matter, Rosenau and Anderson²⁰ had previously pointed

17 Finzi Virchows Arch, 1913, 214, 413

18 Biedl Innere Secretion, 1913, 1, 523

19 Friedman Jour Med Research, 1915, 32, 95

20 Rosenau and Anderson Jour Infect Dis, 1907, 4, 1

out that gastric erosions are not infrequent in guinea-pigs killed with diphtheria toxin, a substance which causes marked adrenal lesions in these animals. The work of Bolton,²¹ who succeeded in producing gastric ulcerations in guinea-pigs by inoculating them intraperitoneally with the serums of rabbits immunized with guinea-pig gastric mucosa or liver, is also interesting. From this brief review of the literature, it is evident that the etiology of gastric ulcer is still a much debated question.

During the course of our work on the hematogenous production of appendicitis we²² were interested to find that the stomach frequently showed hemorrhages into the mucosal and submucosal tissues, as well as the development of erosions of these structures. No effort was made to select the organisms as far as their focal source was concerned and it was found that eighty-five of the 125 rabbits treated with a variety of organisms showed the described alterations in the stomach. Twenty-six of these animals received pure cultures of green streptococci, including *S. salivarius*, 19, *S. mitis*, 1, *S. fecalis*, 2, and *S. equinus*, 4. Twenty-eight animals were inoculated with cultures of nemolytic streptococci, including *S. pyogenes*, 19, *S. anginosus*, 3, *S. subacidus*, 5, and *S. infrequens*, 1. Eleven animals were treated with capsulated gram-negative bacilli, including *B. acidilactici*, 9, *B. Friedlanderi*, 1, and *B. lactis aerogenes*, 1. Of the remaining animals which showed stomach lesions, 5 received *B. coli communis*, 4 *S. pyogenes* and pneumococcus, 3 *S. pyogenes* and *S. salivarius*, 3 *S. infrequens* and *B. Friedlanderi*, 3 staphylococci, 1, *S. salivarius* and *S. equinus* and 1 pneumococcus. Detailed data are shown in the table.

The lesions in the stomach varied from hemorrhage into the tissues of the mucosa and submucosa to ulceration of these structures. Even in the most severe reaction, the only alteration noted in the muscularis was an inflammatory infiltration, with but rarely any evidence of destruction of the inner muscle fibers. The lesions varied in size from that of a pinpoint to well defined areas 0.3 cm. to 0.5 cm. in diameter. In most cases the hemorrhages were discrete, although at times they were somewhat irregular in outline, with a tendency to become confluent when closely aggregated. These changes occurred in all parts of the stomach, although somewhat more frequently in the cardiac end. The erosions consisted for the most part of flat looking irregular patches, which, many times, were covered by a grayish slough situated on a deeply colored base. At times, however, larger areas of ulceration were seen. A rabbit injected with *Staphylococcus albus* and killed four days later showed a flattened, elongated erosion situated

21 Bolton Jour Path and Bact, 1914, **19**, 258

22 MacCallum A Text Book of Pathology, Phila., 1917, p. 404

23 McMeans THE ARCHIVES INT MED, 1917, **19**, 709

LESIONS IN STOMACH AND OTHER ORGANS

Organisms Injected	No of Animals	Stomach	Appendix	Duodenum	Small Intestine	Heart		Joint	Muscle		Peri Art	Endocardium		Kidney	Thymus
						Hemorrhage	Infiltration		Hemorrhage	Infiltration		Hemorrhage	Infiltration		
S pyogenes	25	19	11	7	5	1	9	11	2	2	2	15	2	3	9
S subvultus	10	5	2	2	1	0	0	1	0	0	1	3	0	0	3
S anginosus	3	3	1	1	1	0	1	0	1	0	1	2	0	1	2
S infrequens	2	1	1	1	0	0	0	0	1	1	0	1	0	0	0
S pyogenes—S subvultus	5	3	3	2	3	0	0	1	1	0	2	2	0	0	3
S pyogenes—pneumococcus	6	4	5	4	3	2	0	1	1	0	1	0	0	0	1
S infrequens—B Friedlander	4	3	3	2	4	0	0	2	0	0	1	1	1	0	3
S subvultus	25	19	11	10	1	1	12	7	1	0	1	11	5	6	8
S equinus	6	1	2	3	0	1	1	0	1	0	1	2	1	1	1
S fecalis	2	2	0	2	0	0	0	0	0	0	0	1	0	0	1
S mitis	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0
S subvultus—S equinus	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0
Pneumococcus	1	1	0	0	0	0	0	0	0	0	1	1	0	0	1
B Friedlander	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0
B acid lactici	10	9	8	7	9	0	0	8	2	2	0	8	0	0	1
B lactis aerogenes	1	1	0	1	1	0	0	1	0	0	1	1	0	0	1
B coli communis	5	5	2	3	2	0	0	1	0	0	0	1	0	0	4
Staphylococcus	3	3	2	1	1	1	1	0	0	0	0	1	1	0	1
	111	85	55	17	35	12	24	18	13	5	15	65	12	11	15

FOURTEEN ANIMALS NOT WITHIN THE GROUPS THAT PRESENTED STOMACH LESIONS

S subvultus	6	0	2	3	0	0	1	0	1	0	0	2	1	0	1
S pyogenes	3	0	1	0	0	0	0	0	0	0	0	0	0	0	0
S mitis	2	0	1	1	1	0	0	0	0	0	0	0	1	0	0
Staphylococcus	3	0	3	2	2	0	1	0	0	0	0	1	1	0	1
Total	125	85	62	53	18	12	26	18	14	5	15	68	15	11	17

on the greater curvature near the cardiac opening. The base of the area was clean and light pink in color, with a number of dark hemorrhagic spots scattered through it. The borders of the ulcer were sharply defined.

Microscopically, varying degrees of reaction were observed. The most frequent alteration consisted of hemorrhage into the mucosa and a hyaline-like degeneration of the folds, with a slight infiltration of leukocytes and lymphocytes. The deep mucosa and remaining layers of the stomach wall were free. Again, the hemorrhage was more deeply situated in the region of the muscularis mucosa, and showed a loss of structure in the overlying mucosa, although at times the general hyaline outlines of this layer remained. In these areas there was a more marked infiltration of leukocytes, with, at times, many cocci distributed throughout the area. An animal injected with *S. pyogenes* illustrated the most severe type of reaction observed, and a microscopic description of these areas will serve to illustrate the third and less frequent degree of change. Sections of this animal's stomach showed an alteration which involved the layers down to the muscularis, but had left this coat unchanged. Over quite an extent, the mucosa was broken and eroded with islands of gland structures still to be seen between areas where the structure of the mucosa had been destroyed. In a large part of the area the mucosa was completely destroyed and replaced by an exudate of fibrin and leukocytes which extended into the muscularis in one place along the course of a lymphatic channel. The cells of the submucosa were swollen and increased in number. Along with the leukocytes, a number of eosinophils, lymphocytes and a few plasma cells were seen. Save for the large ulcerated areas, the reaction in the deeper tissues in other places had a patchy appearance not unlike areas of focal necrosis. A large amount of hemorrhage was distributed in the superficial tissues.

The frequency with which spontaneous ulcerations occur in the stomach of rabbits has not been definitely determined. Stewart and West,¹³ however, found spontaneous ulcers in the stomachs of four guinea-pigs, and believed from their observations that the incidence was not higher than 1 in 25 or 30. In one of our rabbits, two ulcerations were found in the pyloric ring. These areas had a punched out character and were covered with a yellowish adherent stringy material. One was an elongated erosion measuring 0.6 by 0.2 cm. when held open by pressure from the serosal side. This area, however, appeared as an elongated slit running in the pyloric ring when the edges were at rest. The other ulcer formed a round punched out pit measuring 0.3 cm. in diameter, and was readily recognized without manipulation. Microscopically, there was complete absence of the mucosa, forming an eroded area covered by fibrin and necrotic debris, throughout which

leukocytes and lymphocytes were scattered. The base of the ulcer rested in the muscularis where there was a marked proliferation of connective tissue, within which bundles of muscle cells were seen. Large numbers of eosinophils and some lymphocytes infiltrated this tissue. The edges of the ulcer were not undermined. In some respects, the ulceration just described resembles the more advanced lesions observed at times in animals which survived the intravenous inoculation for twenty-four to forty-eight hours. In the latter animals, however, the erosion did not extend as deeply into the wall as the spontaneous type described, and there was no attempt at healing as observed in the latter type. Thus, with a definite case of spontaneous ulceration at hand, it would be somewhat difficult to entirely exclude those advanced erosions not associated with hemorrhage from this class. Further, the presence of a single ulceration of this type without other evidence of injury to the gastric mucosa should be looked on skeptically as being caused by the treatment given the animal. Of first importance is the fact that deep involvements of the wall are uncommonly noted in this type of experiment in that the process is essentially one of hemorrhage followed by superficial erosion.

The changes noted in the duodenum were very similar to those observed in the remainder of the gastro-intestinal tract, save for the fact that the erosions were not as marked as those found in the stomach. The entire gastro-intestinal tract was commonly the seat of hemorrhage and presented this picture in the following order: stomach, appendix, duodenum, small intestine, cecum and large bowel. Hemorrhages occurred in the duodenum fifty-three times following the injection into rabbits of a variety of organisms that were in no instance selected with a view to demonstrate localization in this organ. Even in the most severe form, the reaction in the intestinal tract did not present more than a slight erosion of the mucosa. Frequently, however, there were quite extensive hemorrhages into the submucosa and Peyer's patches.

Whether or not these lesions can be compared with peptic or round ulcer as it is observed in the human is a much debated question. Lesions similar to those which occur in rabbits in this type of experiment have been described in human hemorrhagic disease by a large number of writers. Furthermore, they have also agreed that there is no single organism which can be named as the exciting cause of hemorrhagic disease. Regarding stomach lesions of the type in question, Thorel was of the opinion that they were never found in otherwise healthy individuals, but always in those individuals suffering with a general infection. It is on these points that we wish to lay particular emphasis. We have succeeded in producing hemorrhage and erosions of the gastric mucosa in rabbits by treating them with a variety of

organisms, and in all there were other evidences of a general infection. Hemorrhages were the prominent feature in other organs of the body, although, just as in the stomach, an inflammatory reaction occurred not infrequently. The ultimate outcome of these lesions is difficult to determine, in that one is not afforded the opportunity of studying them at varying periods. It seems, however, that these lesions disappear spontaneously in the majority of cases, and there is no definite evidence to support the idea that they burrow deeply into the stomach wall, in that all of the lesions noted were superficial in type, and as a rule did not extend beyond the inner layers of the submucosa. The stomach mucosa, no doubt, has a great power for healing, and it would appear that other tissues besides the mucosa are injured in the production of chronic ulcer of the stomach, as it is observed in the human. MacCallum²² has removed a large part of the stomach mucosa of dogs, and on later examination found the mucosa entirely intact. This observation agrees with that of Best, who found that healthy mucosal cells contain a substance that guards them against digestion. In this case, healing would occur from surrounding healthy cells by extension in a manner similar to that observed in other epithelial covered surfaces. Further, Nauwerck found that the cells underlying the gastric mucosa are very resistant to the action of the gastric juice. The digestion of the small areas of mucosa in the stomach deprived of nutrition by an underlying hemorrhage occurs rapidly, due to the action of the gastric juice, and these small pits are frequently found filled with a chocolate colored blood. With the removal of the impaired tissue by the action of the gastric juice, the surrounding healthy cells undertake the task of repair. From our own observations, and the evidence which we are able to gather from the literature, we do not believe that these lesions represent the initial stage in the development of a gastric ulcer as it is observed in man. The finding of what appeared to be a spontaneous gastric ulcer in a rabbit supports this view, in that the experimental lesions and the spontaneous lesions were very dissimilar. Such lesions cannot be justly compared with the usual type of gastric ulcer observed in man, in that the strenuous methods employed exert a far more widespread influence on the tissues of animals than is ever found in humans suffering with gastric ulcer. They more nearly approach the appearance of the human gastric lesions which occur during the course of a general infection, and are but one of the several manifestations of such a disease. Furthermore, we cannot support the view of elective affinity expressed by Rosenow, in that we have observed with equal frequency hemorrhage and erosions of the stomach of rabbits following the injection of various organisms obtained from indifferent sources.

AUTHOR'S NOTE This work was carried out under the direction of Dr John A Hartwell, to whom I am much indebted for advice and assistance.

BOOK REVIEW

DIFFERENTIAL DIAGNOSIS Presented through an analysis of 317 cases, by Richard C Cabot, M D, Assistant Professor of Clinical Medicine, Harvard University Medical School, Volume 2, Edition 2. Octavo of 709 pages, 254 illustrations. Philadelphia and London W B Saunders Company, 1918. Cloth, \$6.00 net.

In the present volume of this popular work Dr Cabot presents in his clear and forceful manner a series of cases illustrative of several important and common signs and symptoms encountered in clinical medicine. The book is apparently the outgrowth of a smaller manual so successfully employed by the author in case teaching in the Harvard Medical School and case reports used in clinical pathologic conferences conducted at the Massachusetts General Hospital.

The signs and symptoms, which include abdominal and other tumors, vertigo, diarrhea, dyspepsia, hematemesis, glands, blood in the stools, swelling of the face, hemoptysis, edema of the legs, frequent micturition and polyuria, fainting, hoarseness, pallor, swelling of the arm, delirium, palpitation and arrhythmia, tremor, ascites and abdominal enlargement, form the subjects of the several chapters. The records of the Massachusetts General Hospital have been exhaustively searched for clinical conditions in which the subjects of the various chapters were prominent features and the results tabulated in an imposing manner in the order of the frequency of their occurrence in the various diseases. The tables appear at the beginning of each section and are accompanied by a brief discussion of the importance of the particular sign or symptom in question in disease entities. The discussions are characteristically clear and concise and leave no doubt in the reader's mind as to the author's opinion on the topics taken up. His remarks on the significance of dyspepsia are particularly good and should be valuable as an aid in the differential diagnosis of stomach disorders.

Throughout the book there is a tendency to be dogmatic and to give undue emphasis to the value of statistical methods in clinical medicine. One receives the impression from reading the discussions and case reports that diagnosis in medicine usually is not difficult. Most diagnostic problems may be divided into three groups: one group in which the diagnosis is easy, a second group in which the condition is most certainly one of two or three things, and it is in this group that the most skill is required to make an accurate diagnosis. In this group it is necessary to bring together all the possible available data for careful consideration in the light of experience and knowledge. The author rightly emphasizes the importance of keeping in mind the presenting symptoms in these cases. It is, however, dangerous to rely too much on the relative frequency of the occurrence of any particular symptom to influence one in diagnosis. The general picture is necessary. In the third group are placed those cases in which the evidence is insufficient to make a definite diagnosis. The cases are numerous, varied, well chosen and admirably presented for the most part.

One feels at times that completeness has been sacrificed to clearness and brevity.

On page 43 Dr Cabot expresses a certain skepticism as to the ability of the "scientifically trained" physician to evaluate adequately subtle histories. In

reply to this, attention may be called to the statement on page 28, Case 1, where the Abderhalden test is spoken of as a distinct aid in the diagnosis of pregnancy. The Abderhalden test has some years since been proved by the "scientifically trained" physician to be unreliable as a diagnostic of pregnancy.

The book is most attractively assembled, has frequent illustrations, with good cuts, allowing of no confusion concerning the physical signs, and is particularly free from typographical errors. It fills a very distinct and important place in third and fourth year teaching as a book for collateral reading in connection with this particular work.

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A CLINICAL STUDY OF THE FREQUENCY OF LEAD, TURPENTINE AND BENZIN POISONING IN FOUR HUNDRED PAINTERS¹

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While medical textbooks constantly emphasize the fact that lead is one of the chief agents causing the development of degenerative diseases of the heart, blood vessels, kidneys, nervous system and other organs, there is, however, an accumulation of evidence that in practice this teaching is all too frequently ignored or forgotten. Health officers, particularly in the larger industrial centers, have exceptional opportunity through their study of the causes of death assigned in death certificates, through the reports of hospitals, institutions and private physicians, and especially through inspections of factories and the medical examination of workers, to appraise the importance of lead as a cause of disease. One who makes such studies cannot escape the conclusion that many workers in the great varieties of industries in which lead is employed are injuriously affected by it, but do not seek medical care until they have suffered a severe breakdown, frequently, too, complaints of such persons are treated without being recognized as due to lead poisoning.

This study of painters was undertaken to obtain a more concise idea of the extent to which actively employed workers, most of whom thought themselves in excellent health, gave evidence of damage inflicted by lead paints. The apparent frequency with which tuberculosis in painters, printers and other lead workers who came under the notice of the New York City Department of Health seemed to be associated with exposure to the effects of lead was another reason which led to this study.

For several months, leaders of the various local unions of painters were consulted, and through their efforts an opportunity was obtained to secure the consent of members of the respective labor bodies to be examined. The fear and misgiving that the information derived from this study might serve some other than the announced purpose of framing sanitary measures for safeguarding the health of the workers

* Submitted for publication May 4, 1918

¹ Since the writing of this report, nearly thirty other painters have been examined with results that are in accord with the findings reported in the study.

had first to be overcome Through the agency of the officers of the Brotherhood of Painters, 20,000 educational circulars were distributed, in which the dangerous effects of lead, turpentine, benzine and other agents employed by painters were detailed These served to prepare the way Painting is a seasonal occupation, and therefore only a relatively small number of examinations could be made during the fall and winter months When work slackened, and during a period when a strike had been declared, comparatively large numbers of workers presented themselves for examination at the Occupational Clinic of the Division of Industrial Hygiene Those examined were typical of the entire craft No effort was made to select special groups according to age or other special distinction They apparently represented the intelligent and interested members to whom the possibility of improving sanitary conditions appealed, and they came in response to the solicitation of the union leaders All of these painters were employed in interior painting and decorating, some of them doing wall-paper hanging from time to time There were no sign painters, carriage, or structural iron work painters among them

The examinations were made with very few exceptions only by those members of the medical staff of the Occupational Clinic whose medical skill and competency had been carefully ascertained in connection with the other routine work of the clinic These physicians,¹ to whom grateful acknowledgement is due for painstaking and conscientious work, were first given typewritten instructions prepared by me after study of authoritative works, in which the etiologic factors and the symptomatology of poisoning by the chemical agents used by painters were fully described The physicians were urged to make the examinations thorough and deliberate, and an average of nearly an hour was given to each case

Before entering on a description of the trade processes and of the clinical findings obtained in this study, a few words of explanation are necessary as to the reasons for adopting the classification which will be adhered to throughout Sir Thomas Oliver,² gives an appraisal of the relative values of the lead line, basophilia, constipation, colic, anemia, and the presence of lead in the urine It may here be pointed out that Oliver's estimate of the value of lead in the urine as a diagnostic aid, contrasted with that of Dr W Gilman Thompson,³ is so much at variance with the latter that it may be of interest and value to place the two beside each other

1 Drs Charles Pines, Ray Robinson, I E Kahn, J D Benjamin, Leopold Adams, George Mosher and William Adler

2 Reprint of lectures delivered before the Royal Institute of Public Health in discussing "What Constitutes Lead Poisoning?" Paul B Hoeber, New York, 1914, p 197

3 The Occupational Diseases

Thompson says

Authorities differ strangely as to the frequency with which traces of lead are demonstrable in the urine in chronic cases. Oliver believes the test to be very positive, and consequently of great value. My own experience corresponds with that of many French and German writers, who find it very infrequently

Oliver, on the other hand, says

I have not found basophilia the help it has been to other physicians. Personally, I rely more on the detection of lead in the urine. Its presence therein is an indication that the metal is in the system and is being eliminated. On the other hand, lead may be found in the urine of lead workers without the men betraying plumbism. These men are on the borderline. Let the elimination be checked, and symptoms at any time may arise. The presence of lead in the urine occupies the same relationship to saturnism as Koch's bacillus does to tuberculosis, Eberth's bacillus to typhoid fever, and Klebs-Loeffler bacillus to diphtheria.

In other words, a person showing lead in the urine is a "carrier" of lead, not in the sense in which that term is ordinarily employed—that he may convey the disease to others—but in the sense that plumbism is latent, and that any disturbance of the balance maintained by the elimination of lead in the urine and feces may precipitate active manifestations of lead poisoning. Or, better still, Oliver⁴ compares persons with lead in the urine, but without physical signs, to a person with chronic valvular disease of the heart in whom muscular compensation has not broken down. Through the earnest cooperation of Mr. Halsey Durand, chemist, attached to the Bureau of Food and Drugs of the Department of Health, who made the analysis for lead in the urine, we obtained verification of our diagnosis of plumbism so frequently, that we could not help agreeing with Oliver's conclusions. In this report, therefore, the cases are classified in four general groups as follows:

1 Active or positive cases of lead poisoning. In these, the clinical symptoms speak frankly for lead poisoning. These cases are subdivided into two classes: those in which the diagnosis was made on the basis of clearcut clinical symptoms alone, and those in which in addition to such clinical evidence, lead was found in the urine.

2 Latent, inactive, or laboratory positive cases. In these the symptoms were few, but lead was found in the urine.

3 Doubtful or borderline cases. In these the clinical findings were suggestive.

4 Negative or normal cases.

Further, a word of caution is in place because of the classification here adopted. Because special emphasis is given to the incidence of plumbism, the importance of turpentine and benzine poisoning, and diseases of various organs should not be overlooked.

⁴ Bulletin 95, U. S. Bureau of Labor.

CHEMICAL AGENTS AND THE METHODS OF THEIR EMPLOYMENT

Only such facts will be given here as to the kinds of material handled by painters, as may be necessary for a general understanding of the type of poisoning or other disease effects which they might produce. For a thorough and detailed analysis of the methods of work and the character of the chemical agents employed in the painter's trade, the reader is referred to the excellent monograph of Dr Alice Hamilton⁵. Acknowledgment is here made of the service which this bulletin has given in the preparation of this section of the report.

From a clinical standpoint it is sufficient to know that the following are the chief chemical substances used in the mixing and application of paints: lead, turpentine, linseed oil, benzine or other volatile petroleum products generally spoken of as petroleum spirits, benzol, putty containing lead, amyloacetate and wood alcohol.

The lead pigments which are most used are, in the order of their commercial importance

- (a) White lead, or basic lead carbonate
- (b) Sublimed white lead, or basic lead sulphate
- (c) Red lead, or lead oxide (used for painting metal or iron work)
- (d) Chrome yellow or chrome green (used for painting wagons, carriages, etc.)

While there has been much dispute as to the relative toxic effects of the various forms of lead, it may be accepted as a general rule that lead pigments in whatever form employed tend to induce lead poisoning with slightly varying degrees of rapidity. The colic, constipation, headache, joint and muscular pains, anemia, lead line on the gums, mental and nervous symptoms, especially paralysis or diminished strength of the extremities produced by lead, are too familiar to require more than passing mention. Most lead pigments are now sold mixed with oil, so that the effects of dry lead pigment inhaled or swallowed as dust when mixing paints, are nowadays, and in this country in particular, comparatively negligible. In order to place a sufficiently thick protective covering of paint on a surface, several coats must be applied in succession, especially in work of better quality. Even when applied with care, a varying degree of roughness of surface is left on drying. Before an additional coat is applied, these rough projections and lines must be smoothed down. To effect this, a very considerable amount of sandpapering must be done. *This process liberates large quantities of lead dust and is therefore a most dangerous one.* In Europe, and in Germany in particular, the pumice

⁵ Hygiene of the Painter's Trade, Bulletin 120, U. S. Department of Labor, Bureau of Labor Statistics.

stone used for smoothing this rough surface is wet with water, and where this is impracticable, sandpaper is wet with one of the cheaper mineral oils having a low flash point

Before painting is done it is often necessary to remove the old layer of paint or to smooth it down. This may be done by sandpapering, by the use of so-called "varnish removers" containing benzol, wood alcohol or other chemical agents, or, in the case of metallic objects, the paint may be chipped or burned off. The amount of danger in all these processes is in direct ratio to the size of the room or compartment in which the work is being done, to the excellence of its ventilation, and the adequacy of exhaust or other devices for the removal of fumes of lead in burning paint off, and for the removal of benzol fumes, etc., if the latter are used in confined unventilated spaces. Lately, steel or mineral wool has often taken the place of sandpaper. The use of this wool impregnated, respectively, with steel or glass particles, adds to the effects of the lead dust that is liberated, the irritating effect of these metallic or glass particles on the hands, eyes and respiratory organs.

The danger of inhaling or swallowing lead dust generated by sweeping (especially dry sweeping), by the shaking of dirty drop cloths which are used as covers to protect floors and furniture, as well as from the raising of dust by moving or walking about, or from dusty clothing, is quite apparent.

Finally, the danger from hands, mustache, or beard that may be soiled with lead dust and which are not properly cleaned before eating, are too well known to require lengthy description as sources of lead poisoning. Add to this, lack of care in personal cleanliness, alcoholism, and failure to drink milk as a protective agent before and during a day's work, and the chief modes of entrance of lead into the body are apparent.

Linseed oil is used as a vehicle for lead pigment. For years various investigators, and E. C. Bayly in particular, have contended that the lead and linseed form a combination which, in drying, gives off emanations which Bayly has termed "unsaturated aldehyds." These aldehyd emanations cause headache, retching and vomiting, tiredness and often diarrhea. The addition of turpentine to lead and linseed oil increases the amount of the aldehyd. Bayly argues that lead is a slow-acting poison, whereas these symptoms appear rapidly in any individual, following exposure in a room which has been freshly painted. Many differences have arisen as to the part played by lead in this combination. H. E. Armstrong and C. A. Klein hold that the production of volatile emanations is not peculiar to white lead, but is common to all chemical agents which accelerate drying of paint, and they charge turpentine as being the particular cause of these harmful

emanations Trillat of the Pasteur Institute found, however, that turpentine alone was not responsible for these symptoms, for when he combined turpentine with zinc white instead of white lead, although the amount of turpentine was the same, no symptoms developed, whereas they did appear on exposure to a mixture of turpentine with white lead The weight of evidence seems to show that white lead, linseed oil and turpentine form a particularly noxious combination

Henry A Gardner, writing on behalf of the Paint Manufacturers' Association of the United States, has reported that in drying, paints generate carbon monoxid gas No conclusive evidence has as yet been brought forth in regard to this theory

Another process which deserves attention as a source of lead poisoning is the use of white lead putty to fill in cracks, holes and irregularities This is employed more particularly in painting wood-work where high class work is required When not pressed for time, putty is used, and after a few days, when it has dried, the entire paint and putty surface is sandpapered

Turpentine is used to reduce the lead and oil mixture to the desired thinness or consistency, it also assists in the drying of paint In addition to causing staggering and even unconsciousness, conjunctivitis, skin irritations, nausea and vomiting, von Jaksch has attributed to it headache, dizziness, irritation of the throat and of the bronchial tubes and renal system, dry throat, bronchitis and cough, strangury and bloody urine

Benzin and the petroleum spirits are highly volatile and are mixed with paints, especially the cheaper ones, when quick drying is desired Benzin is sometimes used as a thinner in preparing varnish for use on ceilings before kalsomining The chief symptoms which this group produces, as described by Sommerfeld and R Fischer, are headache, vertigo, nausea, vomiting, cough, irregular respiration, weakness of the heart, drowsiness and cold skin, with twitchings and other nervous symptoms on awakening When these agents are used, it is the practice to shut out currents of freely circulating air because the paint dries too rapidly and produces a streaky effect, painters are therefore exposed to the full effects of the benzin

Benzol, acetone, wood alcohol and amylacetate are the usual ingredients of varnish and paint-removers employed by painters Amylacetate is used considerably as a vehicle for bronze pigment This report will deal little, if at all, with their effects, the subject deserves separate study The men using these agents complain not only of the effects of the fumes, but suffer from severe skin trouble because of the lack of proper protective gloves

NUMBER OF CASES OF LEAD POISONING AND TURPENTINE AND BENZIN INTOXICATION

One hundred and sixty-three, a rate of prevalence of 40 per cent, of active cases of lead poisoning, were found among the 402 painters examined in the course of this study. All of these showed definite clinical signs of plumbism, 72, or 44 per cent, of the active cases of lead poisoning among these painters were found to have lead in the urine in addition to clinical evidence. According to Oliver's viewpoint as to latent or potential cases, there were thirty-five, or 8.7 per cent, of the total number examined who were found to have lead in their urine, without manifest clinical signs. In other words, nearly one-half of all the painters examined, or 48.7 per cent, to be more exact, gave evidence of active or latent lead poisoning.

Just as we have found that it is most exceptional for a brass worker suffering from spelter chills to consult a physician, it is likewise very rare that a painter suffering from the effects of turpentine, benzin or one of the other volatile chemicals used as thinners or driers, seeks medical advice on account of their specific effects. They accept the occurrence of the untoward and serious symptoms produced by these poisonous agents with stoic philosophy and complacency, as if they were the most natural circumstances of their trade and rarely consult a physician when overcome. As a result, it is virtually impossible to make any reliable estimate founded on medical observation and study as to the frequency of intoxication produced by these poisonous substances, or to attempt to differentiate from the clinical histories given by these men precisely which one of these volatile chemicals was responsible in any given case for the symptoms described. In this study no attempt has been made, therefore, to distinguish between the effects of turpentine, benzin, wood alcohol, acetone, benzol, etc. At least 70 per cent of all those examined gave a fairly clear and recognizable history of at least one or many attacks, and 142 painters gave a history of recent severe intoxication, in which several or even all of the following symptoms were noted: a sudden sense of weakness in the legs, irritation of the eyes, difficulty in breathing and dryness and irritation of the throat, cough, headache and dizziness, which in a number of cases was so pronounced that we frequently obtained a history of falls from scaffolding or ladders. In addition, there were often present nausea, vomiting, painful and frequent urination during the day, a few cases of bloody diarrhea, and several others of bloody urine. A number of painters stated, without leading questions, that the urine was subsequently not only very dark, but that it had a very strong and peculiar odor. The verification of these statements must be left to future study. Varnish

removers containing acetone and benzol were reported to have caused severe air-hunger. Most of the painters were emphatic that benzol had caused them more discomfort and illness than all the other volatile agents, its effects seem to be more lasting. A number of very intelligent painters were certain that it had left a feeling of weakness, dizziness and giddiness for one or more days. A few, about seventy in number, who had been at work for varying periods, seemed to enjoy a surprising immunity to the effects of volatile chemicals. Most painters when overcome were quickly relieved when taken into the open air. Some complained that when they went to an open window for fresh air they risked the displeasure of their employer, who charged them with loafing. It was our impression that those suffering from lead poisoning seemed more frequently to suffer from the fumes of these volatile substances. Practically 60 per cent of the recent cases of turpentine and the related type of intoxications were found among our 163 active and thirty-five latent lead poisoning cases, out of the total of 402 painters studied. Forty-seven of the 142 recent cases had suffered from frequent and moderately painful urination. Occasionally, symptoms that indicated strangury with bloody urine were described. Twenty-three of this group complained of frequent attacks of vertigo. The age groups of the painters who were studied were as shown in Table 1.

TABLE 1—LEAD POISONING BY AGE GROUPS

Age, Years	Active Cases		Latent Cases of Plumbism	Border line Cases	Negative Cases	Total
	With Lead in Urine	Without Lead in Urine				
20 to 29	12	23	16	18	71	140
30 to 39	30	36	15	15	57	158
40 to 49	18	20	2	8	21	69
50 to 59	10	9	1	3	7	30
60 and over	2	2	1	3	2	10
Total	72	90	35	47	158	402

It will be seen from Table 1 that a comparatively small number survive as active members of the trade after having attained the age of 50 years. Also, 64 per cent of the active cases of lead poisoning occurred between the ages of 30 and 49 years, whereas seventy-one, or 45 per cent of all those who apparently were free from symptoms of plumbism, were less than 30 years of age. Taken in connection with the facts that most painters enter the trade before their twentieth

year, and being skilled workers, follow it the rest of their lives, and that of the 109 who were more than 40 years of age, 59 per cent were found to be suffering from active or latent plumbism, it seems fair to conclude that the action of lead is slow in asserting itself, but that less than half who have passed the age of 40 escape the disease

Table 2 shows the approximate number of years which those who were examined had spent in the trade

TABLE 2—SHOWING APPROXIMATE NUMBER OF YEARS IN THE TRADE

Years at Trade	Active Cases		Latent Cases of Plumbism	Border line Cases	Negative Cases	Total
	With Lead in Urine	Without Lead in Urine				
1 to 9	10	16	11	20	52	110
10 to 19	28	37	17	14	63	159
20 to 29	15	20	5	8	25	73
30 and over	19	17	2	5	17	54
Total	72	90	35	47	158	402

It will be noted in Table 2 that sixty-three negative cases were engaged at the painter's trade for a period of from ten to nineteen years. On analysis, it was found that most of these were less than twelve years at this work. This table, therefore, seems to emphasize the fact that the heaviest incidence of saturnism is to be found among those who have been painters for ten years or more. Thirty-four per cent of all those examined who had been painters for ten years or more were active cases of lead poisoning, while if one includes latent cases, the number is increased to 42 per cent. Borderline cases, which are those in whom one or more suggestive symptoms were noted, are not included at any time in this report with the active or latent cases, although there can be little doubt that study extended over a longer period of time would have disclosed evidence that would warrant the diagnosis of plumbism in several of this group.

USE OF ALCOHOL

A satisfactory history with reference to the use of alcohol was obtained in only 304 cases. More than 21 per cent of those in whom a history as to alcoholic indulgence was obtained were total abstainers, an almost equal number drank excessively, while about 55 per cent drank very little and only occasionally. We have reason to feel that this information was trustworthy. Alcoholic indulgence, therefore, did not seem in this case to be a marked predisposing factor toward

lead poisoning, as it so frequently has been found. The number of abstainers and of those who drank with great moderation is surprising in view of a number of circumstances that would seem to offer a ready excuse for resort to alcoholic drinks. For example, in buildings that are in process of construction, drinking water is very frequently not provided. Also, in work in occupied apartments, usually of the more expensive sort, inconsiderate housewives, we were told, frequently seem indifferent to the needs of men who are employed to do painting, and appear to regard an effort on the part of the painter to use drinking water or toilet facilities as an unwarranted familiarity or impertinence. It is scarcely to be wondered at that men, under such conditions, should resort to the nearest saloon. Moreover, the parching of the throat caused by turpentine or other volatile substances, produces often a decided craving for something to drink.

TABLE 3—USE OF ALCOHOL AND LEAD POISONING

	Active Cases		Latent Cases of Plumbism	Border line Cases	Negative Cases	Total
	With Lead in Urine	Without Lead in Urine				
Abstainers	15	76	1	2	22	66
Moderate users	29	34	16	19	78	176
Excessive users	20	20	6	6	10	62
Total	54	80	23	27	110	304

PRECAUTIONS TAKEN BY PAINTERS AGAINST LEAD POISONING

Under the head of precautions against lead poisoning may be mentioned the drinking of milk before and during work. We found that while forty-five painters were in the habit of regularly taking one glass of milk per day, and eighty-one regularly drank from a pint to a quart per day, the remaining 276 were extremely lax in this particular. A number of these men were accustomed to start the day's work with extremely little or no food for breakfast. Even of those who habitually drank milk, very few took it before starting work. As a class they seemed unfamiliar with the fact that a moderate-sized breakfast and albuminous food (milk in particular), left little free acid in the stomach to act as a solvent of lead dust that might be swallowed during work.

A total of eighteen out of all those examined testified of their own accord that they could not remove the gross particles of lead from their hands before eating lunch on account of the lack of proper washing facilities in the places where they worked, and that they were in

the habit of taking hold of their food with paper to prevent contamination by their fingers. With very few exceptions, washing facilities for use before eating lunch were of the poorest. The use of a nail brush, or of soap and hot water, was very infrequent. A number of the men used turpentine, and a few used benzine as a means of removing paint from their hands. A large number wore mustaches, but few seemed aware of the necessity of special effort to cleanse these, and especially of the need of cleaning their teeth and mouths before meals because of the dangerous dust in which they were working.

Only seventeen of the total number gave a history of chewing gum, and fifteen of chewing tobacco while at work. One hundred and seventy reported that they habitually smoked a pipe, cigars or cigarettes while at work. It is difficult to say to what degree these factors may have served as a means of carrying lead into the stomach.

Inquiry was made as to whether special facilities were provided to enable the men to eat their lunches in a room free from the presence of lead dust. It was learned that usually the men were compelled either to eat in the rooms where painting was being done, or, in order to avoid eating in such rooms or in dark, out-of-the-way and often even insanitary cellars of a building, a minority went either to a restaurant or more often to the nearest saloon where a hearty welcome, a fairly clean table, and fairly clean surroundings were to be found.

Many complaints were made that owing to lack of lockers for street clothing, these had frequently to be kept during hours of work where they were thickly covered with paint dust.

SYMPTOMS OF LEAD POISONING

Colic—Eighty-seven painters, or 51 per cent of all the active cases of plumbism, gave a history of recent colic. The same complaint was made by three of the latent cases, nine of those who were borderline cases, and eight of the negative cases. Those who complained of colic among the last two groups, in some instances had also other symptoms strikingly suggestive of gastric ulcer or chronic appendiceal inflammation. While a number of the borderline and negative cases had associated symptoms such as backache, constipation, and anemia, which one with an elastic statistical conscience might have been tempted to interpret as cases of plumbism, they were not so classified.

While a number stated that the abdominal pain was localized to the umbilical region, many others described the pain as being of more general distribution. The severity varied greatly in different cases. Some stated that the pain would be repeated often during the day and night but without regularity, others described a definite recurrence of severe cramps at about the same hour each day. Still others described the pain as being of continuous character over a period of

from twenty-four to forty or more hours, with remissions and subsequent return. Twenty-six of the actual cases of plumbism gave a history of repeated attacks of colic during the preceding years, which were accompanied by various degrees of lead neuritis with wrist drop, for which they had to be treated. A surprisingly large number of the positive cases had never sought or received medical advice for this complaint.

Constipation—One hundred and seventeen, that is 72 per cent of the active cases of plumbism, or 29 per cent of all the painters examined, suffered from marked and persistent constipation. In addition, five of the latent cases, nineteen of the borderline cases and forty-three of the negative cases gave the same history. Many of these men stated voluntarily that they would go for days without a bowel movement unless they took a cathartic. Epsom salt seemed to be known particularly to all of them as the cathartic of choice for workers in lead. A small number of the painters were in the habit of taking a daily dose of Epsom salt for short and infrequent periods as a precaution against lead. There is always present the danger that men in this trade will place such complete reliance on the value of Epsom salt as a preventive of lead poisoning as to become totally indifferent to the infinitely more essential measures of dust prevention and cleanliness.

Headache and Other Nervous Symptoms—Seventy-five—about 46 per cent—of the active cases, or 19 per cent of all the painters, complained of frequent and severe headache, usually in the frontal region. The type of headache included under this classification was distinct, according to the history, from the pains in the head which occurred during and immediately after exposure to turpentine, benzine and the petroleum spirits.

Impaired memory and insomnia were mentioned by various painters. No history of encephalopathy, psychosis, or other severe nervous or mental disorders was obtained.

Only three cases of lead paralysis were found in those examined, these were cases of wrist-drop without other involvement. Marked diminution of muscular strength was noted in the right arm thirteen times, in the left arm nine times, and in both arms in forty-six of the active cases. Among the thirty-five latent cases, only one man showed diminished muscular power in the right arm. The latent cases were fairly free from this as also of other characteristic symptoms of plumbism. Very few of the men here studied showed any impairment of muscular power in the lower extremities.

The Lead or Burtonian Line—The presence of the blue line on the gums, said to be a characteristic symptom of plumbism, was in this experience of little significance. It was found in a total of twenty-

two, or a little less than 14 per cent of all active cases, in only one of the latent cases, and in a little less than 6 per cent of all the painters examined. This opinion as to the lack of distinctive value of the lead line has been supported by our subsequent experience in the examination of the gums of many other workers in industries in which large quantities of lead are liberated both as dust and in volatilized condition. Several physicians employed in this vicinity in the medical supervision of large numbers of lead workers share this opinion. Especially in those who are careful as to the cleanliness of their teeth is this symptom infrequently encountered.

Lead in the Urine—Of the 162 positive or active cases of plumbism, seventy-five, or 46 per cent, gave a definite reaction showing lead in the urine. Of the remaining eighty-seven active cases, in only forty could urine be obtained for this test. These were all negative. Since this test was made in only 115 cases of the group of active lead poisoning cases, in reality, therefore, about 65 per cent of all positive cases gave the reaction for lead in the urine. The test, in these cases, was therefore one of very considerable diagnostic value.

The reaction as already stated was obtained in thirty-five additional cases, which, in the absence of active symptoms, were therefore classified as cases of latent plumbism.

Thirty-four of the forty-seven borderline cases had the test applied, the chemist in no case being given any intimation of the clinical diagnosis in any of the tests he performed, and of the thirty-four tests, twenty-four gave what he reported as a "suspicious" reaction, sixty-three negative cases had the test applied, and in these only two "suspicious" reactions were reported. All told, the urine of 247 painters was examined for lead. There was a fairly striking correspondence between the results of this test and the clinical diagnosis.

The assistance derived from the examination of urine for the presence of lead in this study was indisputably of great value in diagnosis.

The test is one in which the technic was modified by one of the chemists of the Department of Health, Mr. Durand, and is of such a character that it undoubtedly cannot be readily performed in hospital and private practice. It is on that account not less valuable than other diagnostic laboratory tests which call for special laboratory skill, such as that of the serologist in connection with the Wassermann test, for instance. The technic of the test is here briefly given.

Technic of Lead Test—After trying the Blyth and several other methods for the determination of lead in the urine, Mr. Durand finally devised a method which gave accurate and fairly delicate results, and yet did away with the boiling over of the tarry mass of urine usually formed in the test, and so made unnecessary that constant watching without which most tests were

spoiled His method is the following 200 to 300 c c of urine are treated with 5 c c of bromin in a porcelain casserole, and evaporated on a hot plate to about 50 c c It is then transferred to a platinum dish and evaporated nearly to dryness, 10 c c of concentrated nitric acid is then added and the evaporation continued to dryness, the residue again moistened with nitric acid and evaporated to dryness The residue is then ignited to a low red heat to burn off carbonaceous matter It is cooled, taken up with 4 to 5 c c water and 2 to 3 gm ammonium carbonate, evaporated to dryness, and the flame played on the dish until the ammonia is driven off It is then taken up with 15 to 20 c c of 10 per cent acetic acid and boiled and filtered hot into a small test tube It is then cooled and 1 to 2 drops of colorless ammonium sulphid and a drop of 25 per cent hydrochloric acid added, and compared with standard samples prepared by adding known amounts of a solution of lead acetate containing 1 gm of lead per 1,000 c c Even less than 0.025 mg gave a distinct reaction

Granular or Basophilic Degeneration of Red Blood Cells—Ever since Ehrlich, and later Grawitz, called attention to the presence of granular degeneration of the red blood cells in cases of plumbism, those who have given much study to this disease have carried on a merry warfare with respect to the frequency with which it occurs in cases of lead poisoning, and with respect to its diagnostic significance A number of observers, such as Hoffman and Schmidt of Leipzig, Behrend, Hamel, Moritz, Embden and Schonfeld have contended for its value, whereas Teleky and Oliver firmly maintain that it is only infrequently associated with plumbism and that its diagnostic value is of no moment, especially since, as the former asserts, it is present not only in anilin and nitrobenzin poisoning, but in pernicious and other forms of anemia, in malaria, and occasionally even in the blood of healthy persons who have not been in contact with lead Biondi, in 1906, stated that he had failed to find basophilic red corpuscles in the blood of those suffering from severe lead intoxication

In the study here reported, the blood of 209 persons was examined for basophilic red cells, with the following results Of 103 active cases, 13, or a little more than 12 per cent, showed stippling, of 19 latent cases, 5, or barely 21 per cent, were reported positive, of 27 borderline cases, only 4 showed basophilic red cells, and of 60 negative cases, only one was positive It would therefore appear justifiable on the basis of this study to say that this sign, like the lead line, is of limited practical value

Anemia—A marked secondary anemia was found in 86 active cases, or 53 per cent In 27 of these cases the percentage of hemoglobin was less than 70, as estimated by the Talqvist scale Among the latent cases 14 patients were found anemic, in the borderline cases 24, and among the negative cases 47 One hundred and seventy-one, or 42 per cent of all painters reported on in this study, showed this condition A very large percentage of the men, according to the clinical description of the medical examiners, had an "anxious, worn appearance"

Arteriosclerosis Heart Affections and Nephritis — Because of trouble with laboratory and clinic equipment urinalysis was performed in only 234 cases, and blood pressure readings were recorded in 232 individuals

Evidence of arteriosclerosis was found in a total of 63 persons or 26 per cent of those in whom blood pressure observations were made. Thirty-six of these persons who had a systolic pressure of 150 or more were active plumbism cases. Of active and latent cases 44, or slightly more than 39 per cent of those in whom blood pressure records were made, showed a systolic pressure of 140 or over. The remaining 67 painters or 61 per cent of the active and latent cases had a systolic pressure of 130 or less, this was rather surprising but it was noted that most of these cases were among those in the youngest age group and although they had very definite clinical evidence of plumbism, they frequently had a systolic pressure of less than 120. This could possibly be accounted for by the lowering of blood pressure which has been noted in animal experiments as occurring for quite a period of time following exposure to or absorption of lead. The action of lead as has already been stated is a slow one and it is very likely that this low blood pressure is coincident with that period during which fibrotic changes which lead to sclerosis of the vascular system are slowly making headway.

Slightly less than 84 per cent of the painters examined 20 persons in all to be exact showed by the presence of albumin casts and other physical signs, the presence of chronic interstitial nephritis. This is a smaller number than we had expected to find, but in explanation it should be stated that the urine obtained for examination was frequently a casual specimen. It is possible that on this account a number of diagnoses were missed which repeated examinations of a twenty-four hour specimen would have made possible. Of the twenty cases sixteen belonged to the group of active plumbism cases.

Eleven of the active cases presented definite heart irregularities and feeble muscular sounds indicative of myocardial changes. Three cases of chronic endocarditis affecting the mitral valves (mitral regurgitation) were noted among the active three among the latent cases, and three among the borderline cases of plumbism making nine cases in all, there were five additional cases among the negative group.

Backache — This symptom was mentioned by ninety-one men, or 56 per cent of the 162 active cases. The pains were generally localized in the lumbar muscles. To what degree it may be the result of overuse of this particular group of muscles as a result of postural strain in working on ladders, or whether it is due in part at least to the local effect of lead it is difficult to say. There were five cases of backache in the latent group thirteen in the borderline cases and

fifty-two among the negative cases who complained of this symptom. Many of the painters complained of pain in the muscles of the calf and the thigh muscles as well. Dr Koelsch of Munich, and other German authorities, are disposed to regard all forms of muscular and "rheumatic" pains as due to exposure to extreme cold in painting buildings in the process of construction. The painters in this group were not so exposed.

The Wassermann Reaction—Much debate has centered about the influence of plumbism on the Wassermann reaction. This question was brought forcibly to the fore in 1914 by Oettinger, Pierre-Louis, Marie and Baion. Cyrus Field⁶ reported five out of twelve cases of plumbism in which he obtained a positive Wassermann reaction. Oliver says that in lead patients he only obtained a positive reaction where he had reason to believe that in addition to plumbism there was a syphilitic taint. In this series of cases, of the 162 painters who had active manifestations of plumbism, only ten, or about 8 per cent of a total of 124 who were tested, gave a positive Wassermann reaction, and in four a doubtful reaction was reported. In each case, however, a history of syphilis or other ground for suspecting syphilis was found. While a positive Wassermann reaction was obtained in ten of the active plumbism cases, the total number of cases belonging to the active group which admitted specific infection was thirteen. Among the other three groups of painters included in this study who were classified with reference to the presence of plumbism, the results were as follows:

In eighteen of the latent plumbism cases which were tested, 2 gave a doubtful Wassermann reaction, of 35 borderline cases the laboratory reported only one positive case, of 99 negative plumbism cases in which blood was obtained, 8 were positive, 2 doubtful and 89 negative. In other words, the test was performed on 272 painters, of whom 120, or 44 per cent, were active cases of plumbism, with a total result of nineteen positive Wassermann reactions and four doubtful reactions.

Miscarriages of Painters' Wives—It has been repeatedly said that the wives of men who were the subjects of plumbism, were in many instances sterile, or, if they became pregnant, they miscarried, or, finally, if a live child was born, it survived but a short time or was much underdeveloped. No doubt, miscarriages have been frequent among other groups of workers in lead, especially those who, like potters, carry on work at home, making the domestic environment unsafe as regards exposure to lead dust. The marital history obtained from 124 of the active showed that 116 were married, and seven single. Among the wives of these 116 painters, according to the statement of

6 Field, Cyrus Jour Am Med Assn, 1913, p 1681

the latter, there had been a total of 340 pregnancies. The number of children living at the time of the examination was 257, the number of miscarriages was 70, and the number of children who were either stillborn or who died from diseases of childhood was 13. About 20 per cent. of all pregnancies ended in miscarriage.

Of nineteen latent cases, 17 were married, and 2 single. The wives of these painters had a total of 28 pregnancies, with 19 living children, 6 miscarriages and 3 deaths.

Of 46 borderline cases, 36 were married and 10 single. The wives of these 46 went through a total of 67 pregnancies with 45 living children, 7 miscarriages, and 15 deaths.

Of 153 negative cases in which a marital history was obtained, 53 were single. (The unduly high proportion of single men in this group is indicative of their belonging to the earlier age groups, painters as a class, judged by this experience, marry at a fairly early age.) The wives of the 100 married painters in this group went through a total of 205 pregnancies with 174 living children and 24 miscarriages.

Loss of Weight and Muscular Strength.—This was a surprisingly common complaint. In seventy of the active cases it was very marked, the loss in weight ranging from 8 to 20 pounds in the course of a few years. These seventy cases do not include those men in whom evidence strongly suggestive of pulmonary tuberculosis was obtained.

Digestive Disturbances.—Were frequent among the men. Nausea and vomiting, apart from the digestive upset caused by turpentine, benzine, etc., were emphasized by many in whom no evidence of the toxic effects of lead could be discovered. Fully one third of all painters gave a history of gastric distress, acid eructations, anorexia and nausea, which were especially marked during the season when work was most active. Stimulantism, that is, the resort to alcoholic stimulants, especially by those workers who feel a strong distaste for food, is well recognized and may be looked for where digestive disturbances are frequent. In the experience of the Leipzig Sickness Insurance Fund and in other German funds where records have been kept, digestive disorders rank high among the causes of morbidity among painters.

Arthralgias and So-Called "Rheumatism."—Pains in various joints were mentioned by 51 painters, or 56 per cent. of those who had signs of active plumbism. Among the 240 latent, borderline and negative cases combined, about 20 per cent. gave a history of joint pains. The joints affected were, in the order of frequency, the shoulder, wrist and hip. While these pains were often characterized by the patient as rheumatic, only exceptionally was a history typical of acute articular rheumatism obtained. The arm which was most used while at work seemed to be most often affected.

Dr Frank Koelsch⁷ of Munich, in 1913, submitted an explanation as to the frequency of chronic and acute articular rheumatism and muscular rheumatism among painters, which does not apply to the special group reported on in this paper. Taking the statistics of the sickness insurance funds of various German cities as a basis, he found that these various forms of rheumatism were caused by work in exterior painting, because of exposure to extremes of weather and to draughts while painting buildings which were in the process of construction. The Leipzig Insurance Fund statistics show that painters were affected by these various forms of articular and muscular rheumatism more frequently than persons employed in all other occupations combined.

While evidence of tonsillitis was rarely obtained in our series of cases, this was given as a cause of illness among painters in many of the cases in the Leipzig insurance funds and elsewhere in Germany, this is referred to because of its possible bearing on joint pains.

Pain in the Chest—Fifty-five painters belonging to the group of active plumbism cases complained of a dull pain in the chest. This pain had no typical location, being referred to the front of the chest or to the back on either side. As described by the painters, it did not seem to have the character of a pleuritic pain or "stitch," or so-called pleurodynia. There seemed to be so large a degree of similarity, as judged by description, between the character of pains in the back and those about the joints and over the chest that one got the impression that all three types of pain were myalgic in character, and that the joint pains, so-called, were likewise due to pains in the musculature about the joints.

Metallic Taste in Mouth—Of the 162 active cases of plumbism, thirty, or about 18 per cent, gave a history of having frequently had a distinct metallic taste in the mouth. This sensation did not seem dependent on the presence of the lead line. On the other hand, in all the other types of cases combined, this complaint was made by only four persons.

This concludes the list of essential symptoms elicited in this study with reference to lead poisoning.

PATHOLOGICAL CONDITIONS OF GENERAL INTEREST

Respiratory Affections—Bronchitis and Tuberculosis—A total of ninety-eight, or nearly one-fourth of all the painters examined, gave a history and physical signs of chronic bronchitis. Fifty-eight of these cases were found among those giving evidence of active plumbism. In other words, 59 per cent of all cases of chronic bronchitis were

⁷ Monograph on the Painters' Trade, Hamburg, 1913

found among the cases of active lead poisoning. In view of the fact that an apparently disproportionately large number of cases of tuberculosis in painters were reported to the Division of Industrial Hygiene by the various Tuberculosis Clinics of the Department of Health during the last two years, the frequency of chronic bronchitis may have distinct significance as a predisposing cause.

Dr. Edgar L. Collis⁸ dwells at considerable length on the importance of bronchitis induced by mineral, metallic or other irritant dusts arising in various occupations as established by a number of students of the subject. He presents a very plausible explanation of the tendency of dusts to produce an antecedent bronchitis which creates a special predisposition to either tuberculosis or to pneumonia. According to this theory, if the dust particles which are inhaled are brittle, insoluble and noncolloidal in structure, they tend to produce tuberculosis; otherwise they predispose to pneumonia. May it not be that interior painters, who are exposed not only to lead dust, which does not appear to be irritating, but to the fumes of turpentine, benzine and other volatile irritants as well, are therefore particularly subject to the development of tuberculosis? At all events, the tendency to emphasize the importance of dust, and to overlook the predisposing influence of other irritant agents should be guarded against. The anemia caused by lead absorption, to which painters are so liable, undoubtedly aggravates the tendency to tuberculous disease of the lungs. In all of our cases of bronchitis, a sputum examination was made, but with negative results.

In this series, in two of the active cases of plumbism the men had moderately advanced pulmonary tuberculosis with tubercle bacilli in the sputum. Twenty-eight had signs in the lungs, and of these eighteen, or 45 per cent of the total number examined, were reported as showing evidence of an incipient process, without positive sputum. Five of the eighteen incipient cases gave a history of bloody expectoration or marked hemoptysis, all of these men gave a history of marked loss of weight and strength and were anemic and several gave a history of night sweats. In only about three or four of these cases could a family history of tuberculosis be elicited. The total of advanced and incipient cases was therefore twenty, or about 5 per cent, and inclusive of suspected cases, 30, or about 75 per cent of those examined.

In the Leipzig, and in other German statistics furnished by Koelsch and several times alluded to, bronchitis was found to be one of the most common complaints, and together with various forms of rheumatism said to be due to exposure to cold, diseases due to "catching cold" (*Erkältungskrankheiten*), are said to have constituted 37 per cent of all cases of sickness reported to the Leipzig Sickness Fund. Just as the cases of rheumatism due to exposure to cold were negli-

⁸ Milroy Lectures, 1915, Public Health. September, 1915.

gible, because there were practically no exterior painters in our group of 402, so the cases of bronchitis which were found in this study could not be explained as being due to the effects of extreme cold and drafts

Bronchial Asthma—Seventeen cases of bronchial asthma were found in this series, eight of these were cases of active plumbism

Skin Diseases—Acne, especially on the back and face, and chromophytosis were very frequent. In this report, however, interest is centered in those forms of dermatitis which might be held to be the result of the paints and their ingredients. Twenty-three marked cases of occupational dermatitis of eczematous type, showing as a rule squamous patches, were found. These affected the fingers and hands principally, occasionally the face. Slight lesions were ignored. In a number of cases marked callosities were recorded over the anterior tibial border of the legs, where pressure had been made against the rungs of stepladders. Although a number of painters complained that following the use of turpentine, and varnish removers more particularly, they suffered from a severe inflammation of the hands, which was accompanied by a cracking of the skin and a considerable amount of bleeding, those conditions were not observed in the course of our examinations. This was in all likelihood due to the fact that the men came under our notice during a period when they were without work, and when such lesions would have had ample opportunity to heal.

Teeth—Ninety painters had a fairly marked pyorrhea alveolaris, and 104 showed marked decay of the teeth and lack of care, making a total of 194, or about 48 per cent of all who were examined.

Visual Defect—Only marked defects of vision were noted. Fifty-one such cases were found. Ophthalmoscopic examinations were not made.

Nose and Throat Defects—Chronic pharyngitis was found in 127 painters. Hypertrophic rhinitis was reported in twenty-eight cases, and marked deviation of the septum in 147 painters. In only fifteen was marked hypertrophy of tonsillar tissue found.

Varicose Veins and Flat Feet—Forty-two men had varicose veins and seventy-two showed marked flat foot.

Inginal hernia was present in six cases, while a number who had previously suffered from this condition had been cured by operation.

REPORT ON INVESTIGATION OF HOME CONDITIONS OF ONE HUNDRED FIFTEEN PAINTERS

The criticism is frequently made that tuberculosis, anemia, malnutrition, nervous disorders and other abnormal conditions of health are wrongly attributed to the influence of occupation, when in reality,

insanitary home environment, lack of food, and domestic worries may be responsible for such conditions. In order to obtain definite data with respect to home conditions and their possible influence on health, nurses attached to the Occupational Clinic staff were instructed to visit the homes of all in this series of painters who lived within a radius of about four or five miles of the clinic. The visits were made during the day time. A number of painters had moved to other quarters during the interval between their examination at the clinic and the visit of the nurse, in still other cases the homes were found closed on several occasions, and they were not revisited. In all, 115 painters' homes were investigated. Speaking generally, it may be said that the sanitary conditions were found to be good. Cleanliness, freedom from overcrowding, good ventilation and lighting, a sufficient and varied diet and absence of alcoholic excesses among the members of the families were the general rule. For those who may be interested in the details of the conditions reported in the homes, the accompanying tabulation is given (Table 4).

RECOMMENDATIONS FOR THE PREVENTION OF OCCUPATIONAL DISEASES AMONG PAINTERS

In view of the high mortality and morbidity rates among painters, compared with all others engaged in industry, as determined by authorities in England, France, Germany, the United States and elsewhere, it would seem urgently necessary that strong measures be taken by public health agencies for the protection of workers in this particular trade.

Sumnerfeld in Berlin, Koelsch in Munich, F. L. Hoffman in this country, Is. P. De Rooys of Holland, and Legge of England, have amply demonstrated in their statistical reports and studies the preponderance of disease and the heightened death rate among painters. Dr. John B. Andrews reviewed the deaths from lead poisoning that occurred in the State of New York during 1909 and 1910, and of sixty deaths that were officially reported to the State Department of Labor, he showed that forty-five occurred among painters, thirty-seven of whom were house painters. It scarcely needs more argument than has been presented by those cited above to bring home the full significance of a vigorous campaign to improve the conditions which are undermining the health and hastening the death of thousands of painters.

The remedial measures that suggest themselves may be divided into two general classes: first, public health measures, second, personal hygiene.

Public Health Activities—Public health authorities can never cope with the problem of prevention in any particular field unless full infor-

TABLE 4—HOME CONDITIONS OF 115 PAINTERS

	Active Lead Cases	Latent Cases	Border line Cases	Negative Cases	Total
Number of homes visited	23	43	10	39	115
Number of homes of married men	19	35	9	32	95
Number of homes of single men	4	6	1	5	16
Number of widowers	0	3	0	2	5
Wages per week					
\$12 to \$15	2	0	0	2	4
15 to 20	8	7	0	7	22
20 to 25	11	16	0	25	52
Information refused	5	2	0	0	7
Over \$25	0	18	9	0	27
Length of employment per annum					
6 to 7 months	3	7	0	6	16
About 8 months	11	17	3	11	42
About 9 months	1	13	5	10	29
10 months or over	4	2	0	3	9
Not stated	4	4	0	9	17
Number of children in family					
None	9	23	6	19	60
One	5	5	1	5	16
Two	2	7	1	2	12
Three or more	7	5	2	13	27
Number of children contributing to income					
One in family	1	2	0	0	3
Two in family	0	5	1	2	8
Three or more	1	0	0	2	3
Number of boarders per family					
One	2	0	0	1	3
Two	0	2	0	1	3
Three	1	0	0	1	2
Average weekly income from all sources					
\$15 or less	2	7	0	1	10
Up to \$20	7	17	7	14	45
Up to \$25	6	15	0	15	36
\$25 or over	2	1	0	2	5
No information	3	0	0	0	3
Rental per month					
\$15 or less	5	25	6	23	59
\$15 to \$20	7	8	2	6	23
\$20 to \$25	5	1	2	4	12
\$25 or over	2	1	0	2	5
Janitors, living rent free	3	0	0	0	3
Food					
Quality					
Good	19	38	10	28	95
Fair	1	8	0	5	14
Poor	3	1	0	2	6
Quantity					
Sufficient	18	39	10	31	98
Insufficient	2	3	0	0	5
Indefinitely stated	3	4	0	5	12
Variety					
Good	15	27	10	33	85
Fair	4	0	0	2	6
Poor	3	10	0	4	17
Alcohol consumed in the home					
Excessive	0	0	0	1	1
Moderate	13	16	9	5	43
None	7	23	5	12	47
Indefinitely stated	3	0	0	11	14
General cleanliness					
Good	19	32	10	32	93
Fair	3	8	0	3	14
Poor	1	1	0	3	5

TABLE 4—HOME CONDITIONS OF 115 PATIENTS—(Continued)

	Active Lead Cases	Latent Cases	Border- line Cases	Negative Cases	Total
Ventilation					
Good	16	31	9	27	83
Fair	2	7	1	7	17
Poor	5	4	0	6	15
Lighting					
Good	17	35	9	2	63
Fair	3	4	1	7	15
Poor	3	3	0	2	8
Number of rooms per family					
Three	3	14	0	11	28
Four	14	16	6	14	50
Five or more	4	12	3	8	27
Number of bedrooms					
One per family	7	2	0	9	18
Two per family	6	27	5	17	55
Three or more	3	10	5	10	38
Number of persons per bedroom					
One	3	1	1	12	17
Two	15	34	8	19	76
Three	2	5	1	4	14

As regards a number of items which are included in this tabulation definite statements were frequently not obtainable from the person who was interviewed, for this reason such information was frequently omitted from the tabulation of data just given

mation is obtained as to the extent and prevalence of a given disease and of all circumstances which predispose to its occurrence Just exactly as it is essential for success in the prevention of typhoid fever to have complete reports of all cases occurring in the community in order to be able to ascertain what possible sources of infection may have caused any particular group of cases so it is essential above all things else not only that physicians shall be held legally responsible for the reporting of all cases of lead poisoning that come to their professional notice but employers large and small should be required by law to keep a register of all cases of occupational diseases and of accidents resulting from work which occur among their employees If, by a system of factory inspection and adequate penalties such a law were enforced the frequency of such diseases would become fully known to the public health authorities The particular processes or employments in which such diseases occurred could be definitely ascertained and the proper measures could then be instituted for the elimination of the factors causing such diseases

Aside from such a general measure of control the following specific provisions should be enacted

- 1 The mixing of dry lead pigments with oil or paints while not a frequent source of danger, should not be permitted except when proper provision for the efficient removal of lead dust that may be generated in the process, has been made.
- 2 Dry sandpapering should be prohibited, the use of pumice stone and water, or sandpaper moistened with one of the cheap mineral oils having a low flash point, should be made mandatory

3 When chipping of paint, or the removal of paint by the use of acetone, wood alcohol, benzine, benzol or other volatile poisonous agent is employed, protective clothes and gloves of suitable character, kept in good repair, should be provided by the employer. If this work is done in confined or enclosed spaces, adequate means for ventilation should be provided. The enforced use of gloves in painting, and also in removing paint, would be an ideal measure of prevention, because it is through soiled fingers more largely than through any other source that poison is introduced into the body.

An educational campaign would be necessary among painters to prevail on them to use such gloves if their provision was made mandatory. In an inquiry that was conducted among a limited number of painters, it was found that about 40 per cent did not take kindly to the idea of wearing gloves, though this is entirely practicable for most forms of work.

Lockers or other adequate provision for the protection of street clothes from contamination by lead dust should be made mandatory on all jobs, small or big, whether done in a shop or carried on in apartments. Overalls should be provided, keeping them in good repair and clean is a matter of personal hygiene for which special educational effort would be required. Free access to toilets should be guaranteed to every employee, whether work is to be carried on in buildings which are in process of construction, or elsewhere. Washing facilities and especially hot water, nail brush, soap and towels should be provided by every employer. Many painters who today use turpentine for this purpose because of lack of hot water and other necessities, would gladly avail themselves of such facilities, and that minority which is indifferent to the use of this most important protective measure could be induced to adopt the habit through educational effort.

Lunch-room provision in a place apart from shops or apartments in which painting is done or in which lead pigments are mixed, should be provided on all jobs.

Drop cloths should be frequently changed or washed.

The Substitution of Zinc for Lead—For many years a bitter and confusing debate has been waging between those who advocate the substitution of zinc oxid for white lead, and the champions of the latter paint-pigment. Numerous experiments have been carried on in England and in France particularly, to settle the dispute as to whether zinc oxid is practical for use, especially in interior work, because it is the exposure to lead dust in interior painting that is the most harmful element in the painter's work. In France, certain public buildings have for some years been painted with a zinc oxid paint containing no lead, and have been exposed to various influences of climate and air contamination, with apparently satisfactory results. Had it not been for the present war, a law passed by the French legislature would have gone into effect in 1915 to prohibit the use of white lead in

interior painting. In England the opinion of many master painters seemed equally divided as to the practical value of substitution of zinc oxid for white lead.

Professor Ladd of North Dakota in a letter to the writer in 1916 did not share the faith of those who thought the substitution of zinc oxid was feasible and insisted that personal hygiene was the chief element in the elimination of lead poisoning among painters.

A room in one of the clinics in the Department of Health was painted a year and a half ago with a paint containing zinc oxid without any lead ingredient of any character and while it has not been exposed to fumes or other influences which affect the wearing qualities of paint, it seems to have given good service. It would be manifestly unfair on the basis of this limited personal experience to venture any opinion on this moot question which has engaged the study of the foremost technical experts. One may however express the hope that either zinc oxid may be found feasible and useful as a substitute for white lead in order to diminish the unusually high rate of sickness and death among painters or else that manufacturers of white lead or other lead pigments and employers of labor, will join with public health authorities in an energetic and sincere effort to employ all educational and all other agencies for the safeguarding of the health of the many thousands of workers who are employed in this trade. At present there is no estimate available of the total number of painters in the United States. In the German sickness insurance funds in 1914 it was estimated that over 168 000 men were employed in Germany as house painters: this was exclusive of employers and foremen. This gives some idea of the enormous number whose health and welfare are involved in this trade in every country. If one were to include the numerous industries in which painting is an important essential as a part of general manufacture the number of painters would undoubtedly be very greatly increased.

Labeling of poisonous agents—Every manufacturer of paint in North Dakota and those who wish to sell paint products in North Dakota are made responsible for a definite statement on a label as to poisonous ingredients which the paint mixtures may contain. This law is highly commendable and should be adopted elsewhere. Moreover, the clear labeling of all mixtures placed in the hands of employees by employers should be required so that all poisonous ingredients may be known: and such label should contain a proper warning as to the dangers of such mixture and the method of preventing poisonous effects, and such warning, furthermore should be printed in the language familiar to the particular group of workers who may handle such paint.

The German law provides for many of these safeguards and is clear and explicit about the provision of temporary working sheds for the protection of clothing and for use as lunch rooms. In connection with regulations for the protection of painters during lunch periods, it is important to recognize that the painters who receive a mere half hour for lunch and who are not allowed extra time for washing will be subjected to an overwhelming temptation to omit this most important preventive measure. It should therefore be made mandatory that at least five minutes should be allowed from working time for the use of washing facilities before eating lunch.

Compensation for occupational diseases and for occupational lead poisoning in particular, will do more to safeguard the health and lives of workers than any other single legal or hygienic measure. It should not be delayed.

Personal Hygiene—Personal hygiene is so intimately connected with some of the measures that have already been considered, that it has been unavoidable to make passing mention of them in the course of the recommendations made under the preceding heads. It is most essential, as Richard Miller has pointed out, that workers be made to realize that they are exposed to unusual danger, and that the man who is poor in health and has low powers of resistance, will, in all likelihood, be much more readily susceptible to lead poisoning, to tuberculosis, and other diseases peculiar to painters than one who is well nourished. So dangerous is this trade, and so important is personal hygiene, that a robust and powerful man entering this trade, unless he exercises due care as regards his person, will succumb more readily than a painter having low powers of resistance who exercises extreme care as regards personal cleanliness and general hygiene. Washing of the face, mouth, hands and mustache, particularly before eating, stands as the foremost protection to be taken by painters. By washing is not meant a mere perfunctory exercise, but a thorough cleansing of the hands with hot water, nail brush and soap. It would be manifestly impossible to urge this on painters unless the law compelled the provision of these facilities.

Eating before going to work is a valuable and necessary precaution. Lead seems to be much more readily absorbed from an empty stomach than from one which contains milk or other food. Milk is especially valuable for the purpose and should be taken during the day.

The use of alcohol subjects persons to a greater risk from lead poisoning and makes them more readily susceptible to the effects of turpentine, benzine and other volatile agents.

Painters should be warned against dry sweeping. A moistening agent should be employed wherever this is necessary, and while it has been found practically impossible to induce painters to employ respira-

tors, they should be urged to wear same especially when dust is unavoidably raised in any process

Smoking—Smoking which is regarded as a most innocent habit by the majority of workmen, has a peculiar danger to the painter. It is not the effect of the nicotine or tobacco which is warned against, but it is the unavoidable placing of lead dust in the mouth through the handling of cigars or cigarettes or pipes with lead-stained fingers or through placing tobacco or chewing gum into the mouth with such soiled fingers, that constitutes the grave danger.

When any painter is compelled to use a paint material containing benzine turpentine or other volatile poison in a confined or enclosed space special means for ventilation should be provided or if this is impossible, such employees should work on short shifts being permitted to leave their work for a few minutes to go to a window for relief from the suffocating effects of such dangerous fumes. Those painters doing interior work or working in buildings which are in the process of construction should be particularly careful to wear adequate protective clothing to protect themselves from the effects of draughts and colds.

SPECIAL COOPERATIVE INVESTIGATION OF PAINTING DONE FOR THE CITY OF NEW YORK

Through the courtesy of Dr. Royal Meeker, Commissioner of the Bureau of Labor Statistics of the State Department of Labor, Dr. Alice Hamilton, who has been widely recognized as an investigator of occupational diseases, became interested in making a study together with the writer of the conditions under which painting on public property was done in the City of New York. Complaints had been frequently received and from varied sources, to the effect that many of the conditions which were responsible for disease among painters in various occupations also existed in connection with the painting of much of the public property of the City of New York. A number of the public bath houses, public lavatories, detention quarters for prisoners and other buildings were inspected by Dr. Alice Hamilton, who made a special visit for the purpose in the winter of 1916 and who in some of these visits was accompanied by the writer.

In brief, it was found that practically all of the conditions which obtained in the painters' trade and are encountered in private enterprise were also present in connection with the painting of these buildings. There were corners or closets in many of the buildings in which no doubt painting without special devices for ventilation was bound to cause benzine poisoning. Varnish removers were also in use in a good many instances exactly as they were in connection with private work. In prison quarters it was found that the prisoners who had not had

previous experience in this work, were given painting, sandpapering, scraping, or other work to do which created considerable amounts of lead dust, without having received proper instruction as to methods of protecting themselves against lead poisoning.

The character of the work varied with different types of buildings that were inspected. Again and again, information was brought to us by various painters that the work done under contract for the city in connection with school buildings was often of a character in which large quantities of inferior paint were employed, and in connection with which a larger amount of thinners and driers were employed than with other grades of paint. This, so far as our investigations went, was apparently true in some cases. We were also informed that at various periods the spray method of painting was used in connection with the painting of park benches, although it was impossible at the time of our inspection to verify these facts from personal observation. It is well recognized that the spray method of painting, unless surrounded by safeguards of unusually excellent character, is one of the most dangerous methods and may produce disease as the result of exposure to lead spray and to fumes of turpentine and benzine. The essential fact brought out by the investigation made jointly by Dr Alice Hamilton and me was that industrial hygienic supervision is a most important and useful function to serve, not only in connection with private business, but equally in the multitude of industrial activities of a large city. The strictures made in connection with painting done for the city do not indicate a lessened regard for human welfare on the part of those who are conducting this work, but rather they reflect an indifferent and unenlightened attitude with respect to the health protection of painters throughout all American cities.

139 Center Street

THE PRACTICAL IDENTIFICATION OF ENDOTHELIAL LEUKOCYTES IN DIFFERENTIAL BLOOD COUNTING

FOURTH REPORT OF STUDIES ON THE MONONUCLEAR CELLS OF THE BLOOD¹

F A McJUNKIN, M D, AND ALICE CHARLTON, M A
MILWAUKEE

A method for the identification of endothelial leukocytes in the peripheral blood has been reported by one of us¹. This method, as was pointed out in its description, is not well adapted to routine work on account of the impossibility of bringing all cells into contact with the carbon particles of the suspension employed to determine the phagocytic properties of the leukocytes. The purpose of this paper is to record the application to blood films of an indophenol staining reaction which brings out characteristic cytoplasmic granules in the endothelial leukocytes.

Leukocytes Granule Stain—To apply the stain, a blood film made in the usual way on a 22-mm square coverglass is covered for one half minute with 5 drops of an alphanaphthol-methyl-violet solution in order to fix the preparation, the alcoholic stain is then diluted with an equal amount of distilled water, and the dilute stain allowed to act for five minutes. The preparation is washed with water, dried with filter paper, counterstained for two or three minutes with 0.01 per cent basic fuchsin (Grubler), washed, dried in the air, and mounted in balsam.

To prepare the alphanaphthol-methyl-violet solution, add 0.2 gm alphanaphthol (Merck reagent), 0.015 gm methyl violet 5 B (Grubler) and 0.2 cc hydrogen peroxid to 100 cc of warm 80 per cent alcohol (made from absolute alcohol). The hydrogen peroxid used should contain approximately 3 per cent by weight of the gas as determined by titration with decinormal potassium permanganate.

Reaction of the Blood Cells to the Stain—Nuclei and cytoplasm are colored red, except the cytoplasmic granules in neutrophils, eosinophils and endothelial leukocytes, which are blue. The granules of basophils are of a distinctive red color. The granules of the eosinophils are large and the central portion appears unstained so that these granules have a very characteristic ringlike appearance not seen in the granules of other leukocytes. The platelets take the red stain faintly, the erythrocytes are pink.

Since the red cytoplasm of lymphocytes is entirely free from bluish granules, the only differentiation requiring discussion is that between

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* From the Pathological Laboratory of the Marquette University School of Medicine.

¹ McJunkin, F A. THE ARCHIVES INT MED, 1918, 21, 57.

the neutrophils and endothelial leukocytes. That these two cells have an entirely different origin has been shown elsewhere by one of us²

The character of the granules of the endothelial leukocytes and the relationship between granules and nucleus distinguish them from polymorphonuclear neutrophils. Of these two points, the first is of greater importance. The granules of the endothelial leukocytes are discrete and the cytoplasm is distinctly seen between them, while the neutrophilic granules are so thickly placed that little of the cytoplasm can be seen. The neutrophilic granules are larger and more regular in shape than those of the endothelial leukocytes (Plate, A, B, C). In pathologic blood in which mononuclear myeloblastic cells (neutrophilic myelocytes) are present the character of the granules assumes a greater significance. However, since the granules of neutrophilic myelocytes and of the so-called metamyelocytes are even more prominent than those in the polymorphonuclear neutrophils, there is no chance of confusing myelocytes and endothelial leukocytes, although both are mononuclear. The differential character of the endothelial leukocyte is the presence of blue granules in a mononuclear cell. Although the nucleus of this leukocyte frequently has a broken outline, it does not consist of pyknotic nuclear masses connected by filaments. The reason that endothelial leukocytes cannot be identified in films stained with a polychrome blood stain is that some of these cells, such as the one shown in B in the plate, are entirely devoid of granulation and cannot, therefore, be distinguished from lymphocytes when they approach these cells in size.

Endothelial leukocytes after incubation with carbon suspensions according to the method previously referred to¹ contain carbon. That the carbon-containing mononuclear leukocytes (Plate, D, E, F) react typically to the stain is proof that the cells under consideration in this and previous reports are one and the same.

Since some of the endothelial leukocytes contain no granules when stained with polychrome blood stains, and since they approach lymphocytes in size and shape, reported increases in the nonlymphocytic mononuclear leukocytes must be accepted with qualifications. Increases in the so-called "transitional" leukocytes have been reported in typhoid fever, Hodgkin's disease, malaria, and other conditions by various observers. F A Evans³ found 40 per cent of this variety of leukocyte in a case of secondary syphilis under treatment with salvarsan.

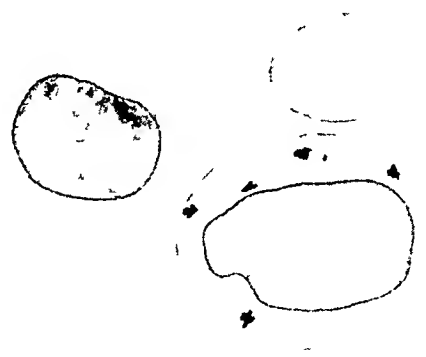
The authors have examined the blood in four cases of syphilis under treatment with preparations of arsphenamin (arsenobenzol brand) with the results recorded in the following paragraphs.

² McJunkin, F A. *Am Jour Anat*, 1918. In press.

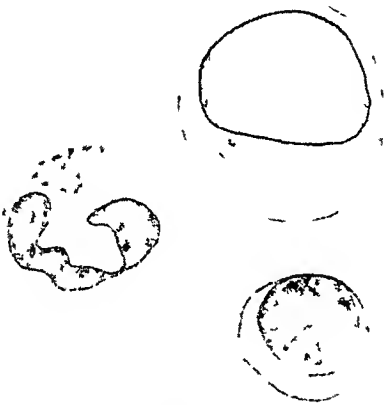
³ Evans, F A. *THE ARCHIVES INT MED*, 1916, **17**, 1.



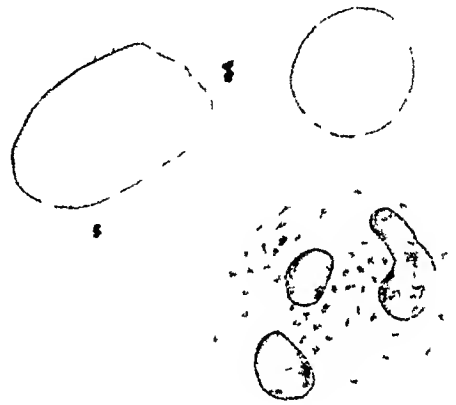
A



D



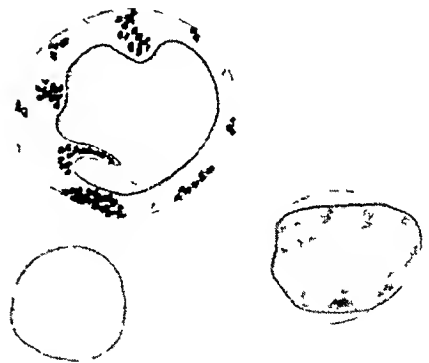
B



E



C



F

L. MASSOPUST '77

REPORT OF CASES

CASE 1—H S, man, aged 21, hereditary syphilis, Wassermann +++ Feb 6 to March 22, 1918, five doses arsphenamin and five doses salicylate of mercury, last dose of arsphenamin seven days before examination of the blood. The blood examination showed 6,950 leukocytes per cubic millimeter, with 7.2 per cent endothelial leukocytes, 60.6 neutrophils, 28.7 lymphocytes, 2.6 eosinophils, and 0.9 basophils.

CASE 2—E S, man, aged 25, secondary syphilis, Wassermann ++++. Two doses of arsphenamin, last dose twelve days before examination of the blood. Blood examination showed 9,650 leukocytes with 6.1 per cent endothelial leukocytes, 56 neutrophils, 34.8 lymphocytes, 2.3 eosinophils, and 0.8 basophils.

CASE 3—J A, man, aged 40, lesion on the tongue, Wassermann ++++. Feb 8 to April 5, 1918, received four doses of arsphenamin, last dose ten days before examination of the blood. The blood examination shows 6,700 leukocytes with 8.35 per cent endothelial leukocytes, 51 neutrophils, 37.24 lymphocytes, 2.02 eosinophils, and 1.39 basophils.

CASE 4—E W, man, aged 29, syphilis ten years previously, at the time of examination there were difficulties in the movements of the left leg and arm, Wassermann "doubtful." April 12, 19 and 26, and May 3 and 10, he received intravenous injections of arsphenamin. The following percentages of endothelial leukocytes were present: April 10, 5.65, April 11, 3.35, April 13, 3.24, April 15, 4.83, April 17, 3.3, April 20, 5.05, April 23, 4.9, April 25, 4.6, April 27, 5.3, April 30, 7, May 4, 6.38, May 7, 6.03, May 11, 4.23, May 15, 4.5. The number of leukocytes varied between 6,200 and 10,600.

In thirty-four differential counts made on the blood of normal adults the average percentage of endothelial leukocytes was found to be 5 per cent, an average of these leukocytes on the seventeen counts made on the four cases of syphilis receiving arsphenamin is 5.3 per cent. The percentages are based on counts of from 1,000 to 2,000 leukocytes. It would seem, therefore, that increases in this variety of cell are not produced by the intravenous injection of arsphenamin.

CONCLUSIONS

The endothelial leukocytes of the peripheral blood can be stained differentially. That the stain is specific is shown by staining blood in which this variety of leukocyte is characterized by ingested carbon.

EXPLANATION OF PLATE

Drawn with camera lucida and oil-immersion objective.

A, B, and C are cell groups from normal blood stained with leukocytic granule stain. A, endothelial leukocyte, neutrophil and erythrocyte, B, endothelial leukocyte, neutrophil and lymphocyte. If it were not for the distinct blue granules in the endothelial leukocyte, it would be difficult or impossible to differentiate it from some of the lymphocytes, C, endothelial leukocyte, erythrocyte, and eosinophil. Note the ringlike appearance of the eosinophilic granules.

D, E, and F are cell groups from normal blood incubated at 37.5 C with a carbon suspension, films stained with leukocytic granule stain. D, lymphocyte, erythrocyte and endothelial leukocyte containing carbon, E, erythrocyte, neutrophil, and endothelial leukocyte containing particles of carbon, F, erythrocyte, lymphocyte, and endothelial leukocyte containing numerous carbon particles that have been ingested by phagocytosis.

I THE BLOOD SUGAR IN THYROID AND OTHER ENDOCRINE DISEASES

THE SIGNIFICANCE OF HYPOGLYCEMIA AND THE DELAYED BLOOD SUGAR CURVE

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It is generally recognized that the thyroid and other endocrine glands exert an influence on carbohydrate metabolism, but a clear understanding of this function has not as yet been reached. Experimental studies of this subject were accordingly undertaken and are reported in this article. They demonstrate that following the abolition of thyroid function there ensues (1) hypoglycemia and (2) a tendency to delayed removal of glucose from the blood, that is, a delayed blood sugar tolerance curve. Clinical studies on hypoglycemia and the blood sugar tolerance were also made in a series of thyroid and other cases. This paper presents a detailed account of these observations which emphasize the value of blood sugar estimations in the study and diagnosis of endocrine diseases.

I Experimental Hypoglycemia and the Delayed Blood Sugar Curve—Previous studies on the effect of thyroidectomy on carbohydrate metabolism have led to contradictory results. Falkenberg,¹ Rahel Hirsch,² also Underhill and Saiki³ have reported diminished tolerance to carbohydrates after thyroidectomy. Eppinger, Falta and Rudinger failed to obtain similar results. Subsequently these authors⁴ and also McCurdy⁵ reported an increased tolerance for sugar after thyroidectomy, with preservation of the parathyroids, in all or in part. Hunter⁶ observed increased sugar tolerance after thyroidectomy in sheep. The chief cause of these discrepancies is the extreme difficulty of performing thyroidectomy in dogs without injury to the parathyroids, which minute organs very probably influence carbohydrate metabolism differently from the thyroid glands. In the work of all of these authors, the tolerance studies have been confined to an exam-

* Submitted for publication March 22, 1918

* From the Montefiore Hospital, New York City. For a preliminary report of this research see Soc Exper Biol and Med, 1917, **14**, 99

1 Falkenberg, W. Cong f inn Med, 1891, **10**, 502

2 Hirsch, R. Ztschr f exper Path u Therap, 1908-1909, **5**, 233

3 Underhill, F P, and Saiki, T. Jour Biol Chem, 1908, **5**, 225

4 Eppinger, H, Falta, W, and Rudinger, C. Ztschr f klin Med, 1909, **67**, 380

5 McCurdy, J. Jour Exper Med, 1909, **11**, 798

6 Hunter, A. Quart Jour Exper Physiol, 1914, **8**, 1

ination for sugar in the urine. Schulze,⁷ however, observed a fall in the blood sugar of patients after thyroidectomy, while in others in whom hyperthyroid symptoms were present a rise in the blood sugar occurred after the operation. McLean⁸ reports a decreased ability of the heart to utilize glucose after thyroidectomy.

1 *Experimental Methods*—It was therefore decided to study the effect of thyroidectomy in animals, avoiding the uncertainty of former investigations by (1) employment of careful surgical technic, (2) by tolerance studies made with the aid of a delicate blood sugar tolerance test, and (3) by using a sufficient number of animals to render the results of value.

The sugar tolerance was tested by a specially devised modification of a similar procedure recently worked out by us⁹ for human subjects. The technic employed was as follows:

Technic—Healthy dogs were placed in metabolic cages and the normal rise in the blood sugar observed after the administration of a definite amount of glucose dissolved in water (6.5 gm glucose per kilogram of animal's weight in 40 per cent solution. No other fluid was given on experimental days). The blood sugar was determined immediately before the ingestion of the glucose then in hourly periods thereafter until the normal level was reattained. The urine was also carefully collected and the twenty-four-hour specimen tested for glucose. On five animals thyroidectomy was then performed by Prof. J. E. Sweet of the University of Pennsylvania, who kindly aided us with his unusual operative skill. In all cases the thyroid glands were carefully removed in toto and the parathyroids, as noted in the protocols, isolated with their blood supply and preserved.

Not all the parathyroid glands described for dogs were isolated in each case, and it is possible that a certain amount of parathyroid tissue was removed with the thyroids. Underhill and Hilditch¹⁰ have shown that two parathyroids can carry out the vital function of these endocrine glands, and in our dogs two parathyroids at least were isolated in every case and preserved with their blood supply, as shown in the protocols. That these glands remained in good condition was demonstrated later at necropsy. Recovery from the thyroidectomy operation took place in each instance without any indication of tetany. The metabolism studies were not resumed for at least ten days after the operation. For these reasons it is believed that in the animals studied, trauma or parathyroid injury may be reasonably excluded. The wounds healed aseptically in each instance, the dogs developing no immediate symptoms which could be ascribed to the operation. Later

7 Schulze, F. Beitr. z. Chir., 1912-1913, **82**, 207.

8 McLean, F. C. Ztschr. f. Physiol., 1913-1914, **27**, 582.

9 Janney, N. W., and Isaacson, V. I. Proc. Soc. Exper. Biol. and Med., Nov. 21, 1917. Jour. Am. Med. Assn., 1918, **70**, 1131.

10 Underhill, F. P., and Hilditch, W. W. Am. Jour. Physiol., 1909-1910, **25**, 66.

some of the animals displayed a tendency to sluggishness and obesity, also an increased susceptibility to infections. The effect of the removal of the thyroid glands on the fasting blood sugar was then determined together with the influence of the operation on the utilization of glucose fed in the same quantities and under the same conditions as before.

TABLE 1—BLOOD SUGAR TESTS ON NORMAL DOGS *

Dog	Before Glucose Ingestion, Per Cent	After Glucose Ingestion		
		1 Hour, Per Cent	2 Hours, Per Cent	3 Hours, Per Cent
1	0.052	0.110	0.103	†
2	0.074†	0.095	0.120	0.075
3	0.099	0.150	0.136	0.102
4	0.102	0.154	0.135	0.113
5	0.080	0.096	0.091	
6	0.111	0.140	0.140	0.113

* Three other normal dog tests are reported in the following table

† Blood could not be obtained

‡ Hypoglycemia of unknown cause in a healthy dog. The curve, however, is perfectly normal.

TABLE 2—BLOOD SUGAR TESTS BEFORE AND AFTER THYROIDECTOMY (DOGS)

Dog	Operation	Before Glucose Ingestion, Per Cent	After Glucose Ingestion					
			1 Hr., Per Cent	2 Hr., Per Cent	3 Hr., Per Cent	4 Hr., Per Cent	5 Hr., Per Cent	6 Hr., Per Cent
1	After	0.072	0.087	0.092	0.095	0.098	0.085	
2	After	0.063	0.076	0.075		0.075	0.065	
	After	0.076	0.145	0.135	0.130	0.120	0.064	0.068
3	Before	0.090	0.130	0.100	0.085			
	After	0.081	0.121	0.109	0.106	0.097	0.079	
4	Before	0.097	0.138	0.111	0.106			
	After	0.083	0.105	0.103		0.093	0.082	
5	Before	0.100	0.164	0.115		0.080		
	After	0.063	0.097	0.102	0.083	0.066		

2 Experimental Results—A marked *hypoglycemia* was found in every case to appear after thyroidectomy, the average decrease in the blood sugar being about 26 per cent. In one instance, Dog 3, the blood sugar was found not to have fallen below the pre-operative level. This dog, however, for some unknown cause, showed a hypoglycemia before operation. The experiment does not stand, therefore, in contradistinction to the others.

Another interesting fact elicited is that following thyroidectomy the feeding of glucose produced a greater *percentile* rise in the blood sugar over the fasting level than occurred when the gland was intact. The actual values representing the *amount of sugar* in the blood following

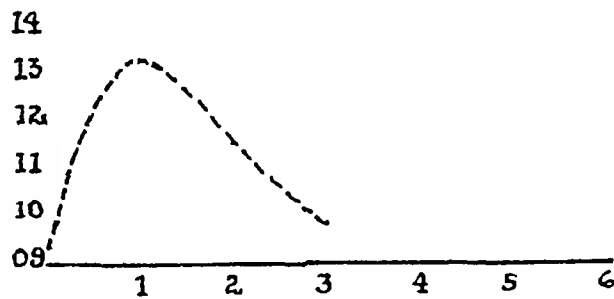


Chart 1—Schema showing the effect of glucose ingestion on the blood sugar. The average curve of nine normal dogs. In Charts 1 to 6 the horizontal line represents the hours and the vertical line indicates the blood sugar in per cent after thyroidectomy, broken line before thyroidectomy.

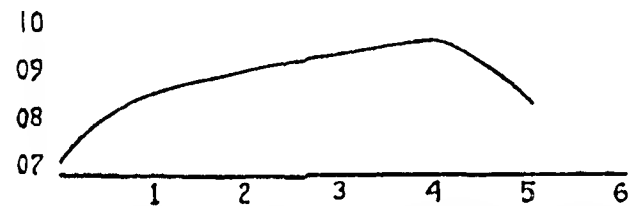


Chart 2—Blood sugar curve of Dog 1. Solid lines indicate the curve after thyroidectomy.

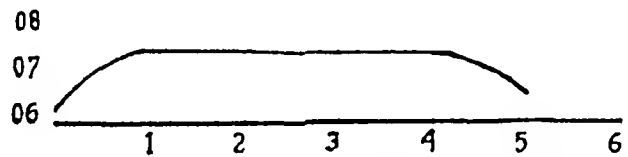


Chart 3—Blood sugar curve of Dog 2 after thyroidectomy.

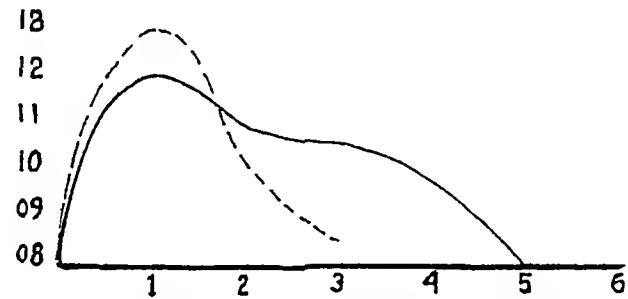


Chart 4—Blood sugar curves of Dog 3 before and after thyroidectomy.

the glucose ingestion were, however, not so large in the postoperative experiments, this being due to the hypoglycemia.

These results are clearly shown in the schemata which also demonstrate that, aside from the hypoglycemia, ingested sugar after reach-

ing the circulation is much more slowly removed than it was previous to thyroidectomy. It is apparent that glucose fed under conditions identical with those before operation required four or five hours rather than two or three hours to vanish from the circulation.

3 *Discussion of Results of the Thyroidectomy Experiments* — These results are of importance from several standpoints. First, they clearly demonstrate the very intimate relation of the thyroid

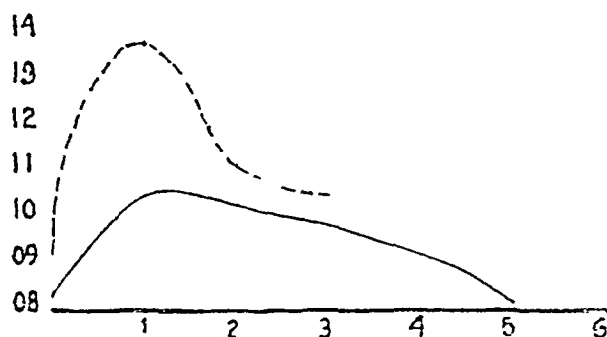


Chart 5—Blood sugar curves of Dog 4 before and after thyroidectomy

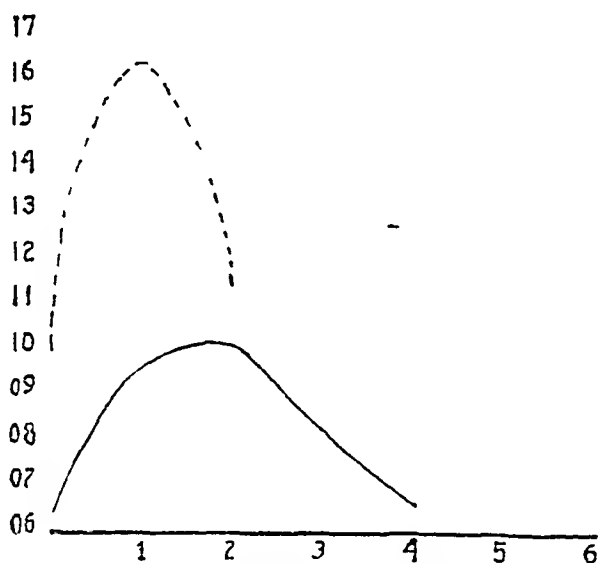


Chart 6—Blood sugar curves of Dog 5 before and after thyroidectomy

to carbohydrate metabolism, as the thyroid evidently functions to maintain the blood sugar at its normal level. Secondly, they show that hypoglycemia follows abolition of the function of an endocrine gland. It is very important to determine whether other ductless glands have the same effect on carbohydrate metabolism. Apparently the suprarenals function likewise, for hypoglycemia has been reported following epinephrectomy¹¹. The hypoglycemia in this instance has, how

11 Bierry, H., and Malloizel, L. *Compt rend Soc Biol*, 1908, **65**, 232

ever, been criticized by Frank and Isaac¹² as being an antemortem phenomenon, because death ensued shortly. Failure of the pituitary function may also lead to hypoglycemia, as will be mentioned later.

It is evident from a study of the protocols and curves that in addition to hypoglycemia a prolonged sugar curve was a result of thyroidectomy in every case. This is of extreme interest, as it seems clearly to indicate that the normal action of the thyroid is to aid in the proper assimilation of carbohydrate.

Reasoning from *a priori* grounds one would not expect delayed blood glucose assimilation coincident with hypoglycemia, for it could be argued that the less sugar in the blood the more readily should glucose be removed from it. It may of course seem rather paradoxical to speak of an increased tolerance existing in conditions in which a delayed blood sugar curve is present. In such a blood condition as just described, urinary sugar tolerance is, however, increased. The deciding factor is the hypoglycemia. It must be remembered that the tendency to delayed assimilation is never so great as to lead to hyperglycemia and glycosuria. Thus, the highest point in the assimilation blood sugar curve of a cretin before treatment was 0.109 per cent. It seems, then, justifiable to regard the hypoglycemia as a possible *cause* for the increased sugar tolerance of these conditions, as determined by the presence or absence of sugar in the urine.

It is possible that the thyroid exerts its effect on carbohydrate metabolism in part, at least, through an influence on the liver. Parhon,¹³ also Cramer and Krause¹⁴ and Kuriyama¹⁵ in careful experiments have demonstrated that the feeding of small amounts of thyroid tissue causes the liver glycogen to disappear. The explanation suggested by Cramer and Krause that the thyroid decreases the glyco-genetic function of the liver seems, however, inadequate, for if this were true one should expect the blood glucose markedly to increase rather than decrease after thyroidectomy. The questions here involved are, however, too intricate for lucid discussion at present.

It is of great importance to determine whether the delayed blood glucose curve observed after thyroidectomy is really due to the loss of thyroid function or whether it is due to other causes. Such a cause might be sluggishness in alimentary absorption, as is held by Magnus-Levy.¹⁶ However, neither this investigator nor, subsequently, others presented any definite experimental proof substantiating this view. We

12 Frank, E., and Isaac, S. *Ztschr. f. exper. Path. u. Therap.*, 1909-1910, **7**, 326.

13 Parhon, M. *Jour. physiol. et Path. gen.*, 1913, **15**, 75.

14 Cramer, W., and Krause, R. A. *Proc. Royal Soc.*, 1912-1913, **86**, 550.

15 Kuriyama, S. *Jour. Biol. Chem.*, 1918, **33**, 193.

16 Magnus-Levy, A., von Noorden's "Handbuch d. Path. des Stoffwechsels," Berlin, 1907, p. 335.

have, therefore subjected the matter to the following test. Former experiments by Janney¹⁷ demonstrated that large amounts of glucose are formed in the organism from the proteins of meat. The sugar excretion following the ingestion of meat by completely diabetic dogs rose and fell nearly synchronously with the excretion of nitrogen resulting from the break-down of the protein constituents of meat. Carbohydrates are known to be formed from proteins under normal conditions, also, the nitrogen of ingested meat is rapidly excreted. Therefore, if we follow the rate of excretion of the nitrogen of meat fed to fasting animals we are able to get an indirect but clear insight into the alimentary rate of absorption of the carbohydrate and protein metabolites of the meat ingested. A weighed mixed diet, including meat, was accordingly fed to a fasting dog before and after thyroidectomy. Nitrogen determinations were made on urinary specimens collected by catheterization at two hourly intervals.

TABLE 3—URINARY NITROGEN EXCRETION CURVE

Operation	Day	Weight, Kg	Period	Nitrogen Fed, Gm	Volume Urine, C c	Total Nitrogen, Gm
Before	1	10.0	24 hr	5.83	*	*
	2	9.9	24 hr	5.83	400	5.35
	3	9.9	24 hr	5.83	428	5.30
	4	9.8	24 hr	5.83	392	5.06
	3		8:30-11:30		60	0.82
			11:30-2:30		200	1.22
			2:30-5:30		68	1.02
			5:30-8:30		35	0.70
			8:30-8:30		65	1.54
After	1	9.2	24 hr	5.83	340	5.74
	2	9.1	24 hr	5.83	387	5.97
	3	9.05	24 hr	5.83	320	5.75
	2		9:20-12:20		22	0.82
			12:20-3:20		120	1.37
			3:20-6:20		60	1.10
			6:20-9:20		65	0.83
			9:20-9:20		120	1.85

Table 3 demonstrates that the urinary nitrogen curve in the athyroid condition is practically the same as before thyroidectomy. For the reasons developed we may hence conclude that alimental absorption is unimpaired in such cretin animals. On the basis of these experiments the delay in the blood sugar utilization curve in our experiments is evidently not to be explained by a sluggish alimentary absorption.

17 Janney, N W Jour Biol Chem, 1915, 20, 321

II Hypoglycemia and the Blood Sugar Curve in Clinical Conditions—In order properly to define hypoglycemia it is necessary to recognize the normal variations in the blood sugar level. In attempting to do this one must bear in mind that the analytic methods for determining the small amounts of sugar present in the blood have only recently been placed on an exact basis. Many observations on the blood glucose in the past are therefore of dubious value. This is particularly true for low values which were formerly reported so frequently, the reason usually being that glycolysis with consequent loss of sugar readily takes place in blood withdrawn from the body. It is probable that on this account wide variations in the blood sugar have been reported for normal individuals even in recent blood sugar studies. During the past few years a large number of blood glucose determinations have been made not only by the writer (N W J) and

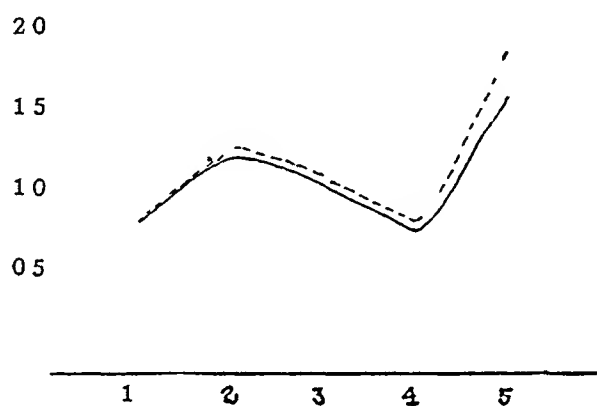


Chart 7—Urinary nitrogen excretion curve before and after thyroidectomy. Solid line indicates before thyroidectomy, broken line after thyroidectomy. The horizontal line represents three-hour periods, and the vertical line indicates the nitrogen in grams.

his co-workers, but also in a number of other laboratories. Although the values obtained are too scattered for proper presentation at present, yet without doubt the great majority in normals range from about 0.085 per cent to 0.11 per cent. We thus come to the original opinion of Bang,¹⁸ whose exhaustive studies on blood sugar caused him to place the normal value at 0.10 per cent, this value being established on the basis of an accurate analytical technic. Occasionally lower values are met with in apparently normal subjects, but in our experience subsequent examinations in such cases have revealed a normal level for the blood glucose. We therefore consider hypoglycemia to be present when values permanently below 0.085 per cent are obtained.

1 Clinical Conditions Showing Hypoglycemia—Hypoglycemia is much less frequently met with than hyperglycemia. In view of experi-

¹⁸ Bang, I. Der Blutzucker, Wiesbaden, 1913.

TABLE 4—DECREASED BLOOD SUGAR TOLERANCE IN ENDOCRINE DISEASES

Patient	Disease	Treatment	Before Glucose Inges- tion, Mg	After Glucose Ingestion					Uri- nary Glu- cose, Gm
				1 Hr Mg	2 Hr Mg	3 Hr Mg	4 Hr Mg	5 Hr Mg	
Y K	Cretin	Before After	65 104	109 164	85 116	85 106	75	65	
M S	Myxedema		96		115	88			
A S	Hypothyroidism		103		130	125			Faint trace
B G	Dysthyroidism		110	180	150	120			
E T	Exophthalmic goiter	Before After	100 70	184 107		105	92		0.75 0
J W	Exophthalmic goiter	Before After	99 122	192 224	151 164	120 130	112		6.13 4.90
J H	Exophthalmic goiter	Before After	70 98	122 138	117 114	91 91	87		1.34 0
M F	Exophthalmic goiter		70	115	107	91	87	74	0
M S	Exophthalmic goiter		88	110	108	86			Faint trace
J D	Exophthalmic goiter		108	181	130	110			
R S	Aeromegaly		134	254	197	140			0
I R	Aeromegaly, mus- cular dystrophy		68	127	95	90	63		0

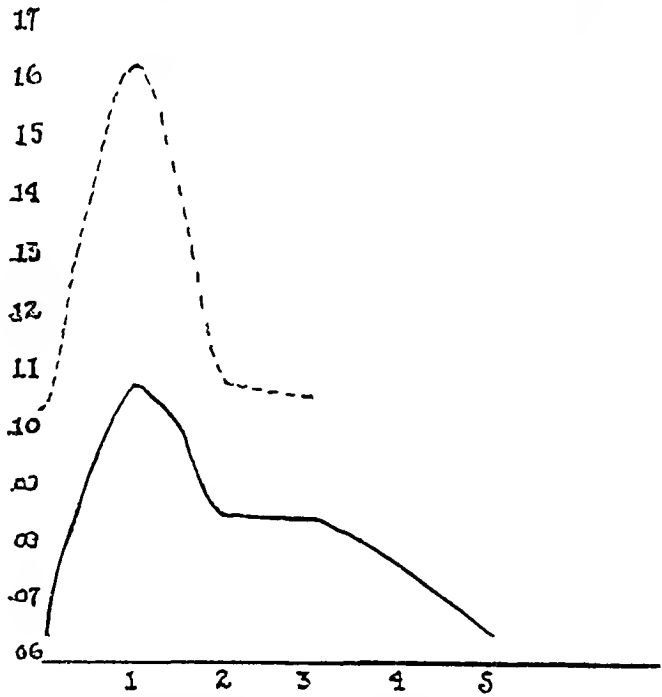


Chart 8—Blood glucose curve in a cretin, Y K, before and after treatment. The horizontal line represents the hours, the vertical line represents the blood sugar per cent, the solid curve line indicates before treatment and the broken line after treatment.

mental observations of a low blood sugar level after removal of the thyroid gland, blood sugar determinations in myxedema and cretinism become of considerable interest. Myxedema cases showing a distinct hypoglycemia have been reported by Geyelin,¹⁹ the sugar values being

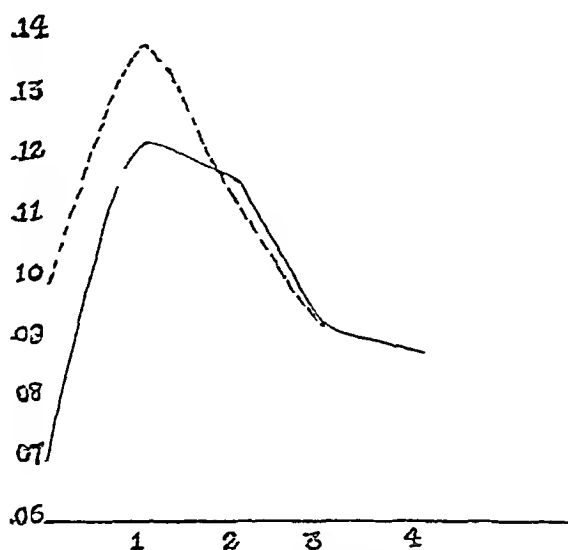


Chart 9—Blood glucose curve in exophthalmic goiter. The lines and figures of the chart have the same explanation as those of Chart 8.

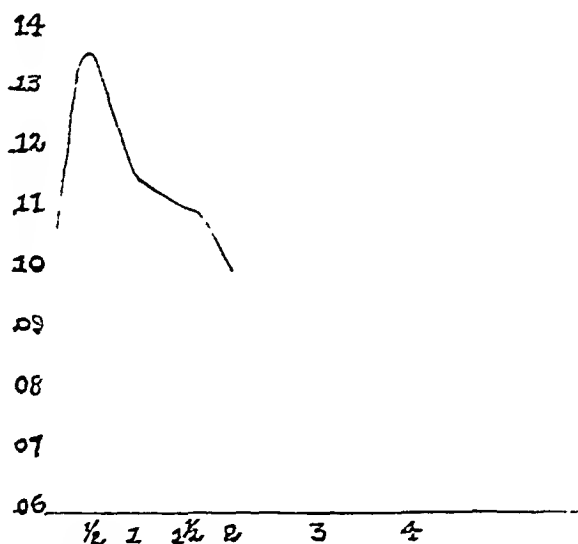


Chart 10—This scheme represents the average blood glucose curve of seventeen normal persons and is reproduced on the same scale for comparison. The blood sugar test was made precisely as in the other human experiments here reported.

0.053 per cent and 0.068 per cent. Two slight cases of myxedema and hypothyroidism in our series showed normal blood sugar values, but a prolonged tolerance curve.

¹⁹ Geyelin, H. R. *THE ARCHIVES INT. MED.*, 1915, **16**, 975.

Our cretin showed 65 and 70 mg of sugar per 100 c c of blood before thyroid was administered. Her case is of unusual interest for the blood glucose curve before treatment was markedly delayed just as was the curve in thyroidectomized animals. After proper thyroid medication practically normal values were obtained for both the fasting level of the blood glucose and for the assimilation curve (see protocols). The high glucose tolerance of Knopfmacher's case²⁰ of cretinism which, after thyroid medication, decreased to normal, finds an adequate explanation in our findings. Similar cases are known in the literature. Various cases of untreated myxedema²⁰ have been reported showing small amounts of glucose in the urine. In such instances the decrease in tolerance has probably developed before the hypoglycemia.

We have recently obtained other new data on hypoglycemia²¹ which was reported at the 1917 meeting of the American Medical Association in a paper on the endocrine origin of muscular dystrophy. This disease, because of certain clinical and pathologic findings which cannot be entered into here, is most probably to be regarded as a symptom complex resulting from failure of proper function of one or more endocrine glands. The blood sugar and various phases of metabolism were studied by us in a representative series of nine dystrophy cases. In every individual distinct hypoglycemia was detected. It is also a striking fact that the majority of the cases showed the same peculiar delay in the blood sugar assimilation curve as was observed in animals after thyroidectomy. Indeed, practically the same metabolic picture was observed as we had been able to produce experimentally by removing the thyroid gland. Thyroid lesions have been reported in several cases of muscular dystrophy. We do not hold the view, however, on this account that muscular dystrophy is necessarily due to thyroid involvement, as hypoglycemia can result from dysfunction of various endocrine organs. Moreover, there is evidence that the pituitary and possibly the pineal gland may also be at fault in this myopathy. Our results seem sufficient, however, definitely to rank muscular dystrophy among the endocrine diseases. Hypoglycemia has been observed by McCrudden and Sargent²² in another case of muscular dystrophy. Addison's disease is known to be associated with hypoglycemia, Porges²³ reporting 0.033 per cent sugar in the blood of one

20 Knopfmacher, W. *Wien klin Wchnschr*, 1904, **17**, 244.

21 Janney, N. W., Goodhart, S. P., and Isaacson, V. I. *Tr Am Med Assn*, June, 1917, *THE ARCHIVES INT MED*, 1918, **21**, 188.

22 McCrudden, F. H., and Sargent, C. S. *THE ARCHIVES INT MED*, 1916, **17**, 465.

23 Porges, O. *Pfluger's Arch f d ges Physiol*, 1912, **154**, 311.

patient Bernstein,²⁴ also Japanese observers,²⁴ likewise observed a low blood level in this disease Janney²⁵ has observed it in a third case, the values obtained being 0.082 and 0.075 in the fasting condition. In hypopituitarism Cushing and Jacobson found hypoglycemia to be present. In view of these clinical findings, persistent hypoglycemia may be fairly regarded as a symptom of hypofunction of the ductless glands. It is very probable that as observations with good analytical methods multiply there will be increasing significance attached by clinicians to the presence of a low fasting blood sugar level.

2 *The Blood Sugar Curve in Exophthalmic Goiter*.—It has long been known that occasionally glycosuria is present in this condition also that there is usually a decreased power to assimilate carbohydrate. More definite information was afforded by Geyelin, who found hyperglycemia in 90 per cent of moderate and severe cases. In mild cases the blood sugar was found to be normal. A slower return to the normal level after sugar ingestion was noted and attention was called to the diagnostic value. Recently Cummings and Piness²⁶ reported a delay in the time taken for the blood sugar to return to its former level after sugar was eaten. Forsbach and Severin²⁷ have also reported a delay in the return of the blood sugar to its former level in tolerance tests on patients with exophthalmic goiter.

The distinctive feature exhibited by our protocols is a very early tendency for a delay to appear in the blood sugar assimilation curve. Thus, Case M. S., which was clinically characterized by but a very mild degree of hyperthyroidism, slight thyroid enlargement, a pulse rate of 90, and mild nervous symptoms, showed a normal fasting value for the blood sugar and only an hour's lengthening of the curve. The blood sugar tolerance test is evidently of more importance than the fasting blood sugar level in exophthalmic goiter, for Case J. H. exhibited a marked prolongation of the curve though the fasting value was originally below normal. We observed a tendency for greater prolongation of the blood sugar tolerance curve in the severer cases. As far as present observations go, the results of the blood sugar tolerance test seem an early and definite sign of thyroid disease, and serve as an indication of the severity of the underlying metabolic disturbance. It is significant that the three exophthalmic goiter patients whose blood was again studied after improvement under hygienic and

24 Bernstein, S. *Berl. klin. Wchnschr.*, 1911, **48**, 1794; Sakoguchi, K., Tatsuya, K., and Kinyosai, O. *Mitt. a. d. med. Fakult. d. k. Univ. z. Tokyo*, 1915, **14**, 3.

25 Janney, N. W. Unpublished observation.

26 Cummings, R., and Piness, G. *THE ARCHIVES INT. MED.*, 1917, **19**, 777.

27 Forsbach and Severin. *Arch. f. exper. Path. u. Pharmacol.*, 1914, **75**, 168.

dietetic treatment exhibited a tendency for the blood glucose curve to shorten and approach the normal (see protocols)

3 *The Blood Sugar Curve in Hypophyseal Disease*—The first case of acromegaly studied by us showed all the usual characteristics of this disease. Enlargement of the lower facial bones and extremities was marked. Bodily strength was fairly well retained. The blood sugar was definitely increased in amount and the tolerance curve markedly delayed. It is remarkable that the blood sugar in this instance, in the absence of nephritis, attained the value of 0.254 per cent in the tolerance test without the appearance of glycosuria. The tolerance is usually decreased in acromegaly, glycosuria being reported in 35 per cent of cases by Borchardt²⁸ in a series of 176 cases. It is exceedingly interesting that a few cases are known in which glycosuria has been succeeded by a marked increase in tolerance²⁹. In these instances, just as in myxedema following hyperthyroidism, hypofunction of the hypophysis is to be suspected. Such a case is that of I. R. (see protocol) which has already been reported in detail in a previous study²¹. Here the symptoms of muscular dystrophy were superimposed on those of acromegaly, giving a very interesting syndrome in which the degenerative features predominated. In contradistinction to the first case, R. S., here marked hypoglycemia is present. The blood sugar curve is delayed in both instances as the protocols show, but glycosuria was absent in both cases.

Diagnostic Value of Hypoglycemia—The experimental studies reported in this article definitely demonstrate that hypoglycemia is a sign of hypofunction of the endocrine glands, the thyroid being taken as an example of these organs. The clinical occurrence of low blood sugar values in diseases representing hypofunctional conditions of ductless glands (cretinism, myxedema, Addison's disease, hypopituitarism) unmistakably indicates the general significance of this symptom. Just how great the diagnostic importance of hypoglycemia will become must be awaited as a result of the accumulation of future studies. It must be remembered that hypoglycemia is occasionally met with in apparently normal individuals (see the foregoing), but this is transitory as far as the few observations recorded permit one to judge. The hypoglycemia in hypofunctional endocrine conditions is permanent. As the metabolic processes are in general more fundamental indications of the actual underlying condition of a given disease than are the more variable and frequently confusingly complex clinical symptoms, the writers are inclined, in doubtful cases, to put consider-

28 Borchardt, L. *Ztschr. f. klin. Med.*, 1908, **66**, 332.

29 Goetsch, E., Cushing, H., and Jacobson, C. *Bull. Johns Hopkins Hosp.*, 1911, **22**, 165.

able weight on the state of the blood sugar. Thus it has been found an aid in the diagnosis of pluriglandular cases presenting a complex and vague symptomatology. Another group in which blood sugar determinations are helpful are those exhibiting a mixture of hyperthyroid and hypothyroid symptoms, attention to which has been called by Bertine³⁰. In the presence of hypoglycemia the hypothyroid side of the case may be regarded as predominating and thyroid treatment is indicated. Hyperglycemia is, on the other hand, a contraindication to thyroid treatment. It must be remembered, however, that some of these obscure cases present a normal blood glucose, which may mean that they have reached midway in their transition from a hyper- to a hypo- condition. One must also bear in mind that thyroid medication used in excess may produce hyperglycemia and even glycosuria.

In difficult cases the blood sugar tolerance test as previously described by us⁹ may be carried out. A prolonged blood sugar curve is an additional indication of endocrine involvement. It is to be remembered that a delayed blood glucose curve is found in both hypothyroid and hyperthyroid conditions.

CONCLUSIONS

Experimental proof that hypoglycemia results from hypo-endocrine function was obtained in the case of the thyroid gland, where hypoglycemia regularly developed after thyroidectomy. Explanation is thus afforded for the low blood sugar value observed in myxedema, cretinism, Addison's disease and pituitary disease and other less clearly defined endocrine conditions such as muscular dystrophy.

The increased tolerance to glucose as determined by testing the urine in such diseases of the ductless glands is probably to be best explained as due to the hypoglycemia present in these conditions.

Delay in the assimilation of glucose from the blood was found to follow thyroidectomy in animals by employment of a blood glucose tolerance test. The same change was demonstrated in cretinism, exophthalmic goiter, and hypophyseal disease. Determination of the fasting blood sugar value and the blood glucose tolerance test are useful in the diagnosis of endocrine diseases.

NOTE. After the completion of this article there was published the report of Hamman and Hirschman (*THE ARCHIVES INT. MED.*, 1917, **20**, 761) of similar studies which corroborate independently many of our observations. This important contribution has unfortunately appeared too late to be quoted in our text.

We desire to acknowledge the assistance rendered by Miss Maude Hays in the dietetic and analytical work of this research.

30 Bertine, E. *Med. Rec.*, New York, 1916, **90**.

II THE INFLUENCE OF THYROIDECTOMY AND THYROID DISEASES ON PROTEIN METABOLITES

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I INTRODUCTION

The endocrine glands undoubtedly play an important rôle in controlling metabolic processes. This field fascinatingly invites research study, both on account of its high scientific interest and its clinical importance. For some time past we have been investigating the influence of the thyroid gland on metabolism. The problems investigated have comprehended the relation of the thyroid to (1) carbohydrate metabolism, (2) protein metabolism and (3) thyroid therapy.

In the present article the influence of the thyroid on certain aspects of protein metabolism are considered. Although it has been known for a long time that the administration of thyroid preparations stimulates protein catabolism, and conversely that the abolition of thyroid function diminishes tissue breakdown, still our knowledge of the influence of the thyroid on specific nitrogen metabolites such as ammonia, creatinin and the purins has remained rudimentary. Better information is here very desirable, since if one could, for example, trace the control of creatinin and purin metabolism to the thyroid or other ductless glands, the curtain obscuring an understanding of the causes of various myopathies and even the gouty diathesis might be raised.

A study of the influence of the thyroid, taken as a type of the endocrine organs, on the nitrogen metabolism is therefore of considerable importance. This problem has been attacked by us from two chief directions. First, we endeavored to learn more about thyroid function by estimating the nitrogenous constituents in the urine of animals before thyroidectomy, and then observing the changes occurring after the operation, that is, the metabolism of experimental athyroidism. Second, the metabolism of experimental hyperthyroidism was studied by following the chemical urinary changes after injecting an overdose of the isolated thyroid hormone. Third, supplemental studies were made in cretinism and exophthalmic goiter, as types of hypothyroidism and hyperthyroidism.

II METABOLISM IN EXPERIMENTAL ATHYROIDISM

1 *The Experimental Plan*—This consisted in making a complete quantitative study, that is, partition, of the nitrogenous substances of

* Submitted for publication April 22, 1918

* From the Montefiore Home and Hospital

the urine of fasting dogs and repeating this examination after removal of the thyroid glands. Before and after the operation, the sparing action of glucose on protein metabolism was simultaneously followed for purposes to be mentioned later. The same precautions to insure accuracy in these metabolic experiments were taken as have been described in preceding researches by one of us and his co-workers¹

In view of the fact that the same experimental subjects have been used in a recent investigation² on the effect of thyroidectomy on the blood sugar, it seems unnecessary to repeat the details here. It may, however, be stated that considerable care was exercised throughout in removing the thyroids and that no parathyroid tetany or other disturbing factors developed. The animals before and after the operation remained in excellent general condition, which fact gives added reliability to the results.

During the experimental periods, both before and after the operation, the dogs received as diet nothing but 40 c c water per kilogram of body weight, except on the sugar days, when 6.5 gm glucose for every kilogram of the animal's weight were dissolved in this amount of water and administered by mouth. By this means the results of the metabolic study before and after thyroidectomy are to be regarded as mutually comparable.

In making the nitrogen partitions the following substances were determined with methods as indicated: total nitrogen, Kjeldahl; urea nitrogen, Van Slyke and Cullen,³ ammonia nitrogen, Van Slyke and Cullen,³ creatinin, Folin and Morris,⁴ creatin, Benedict,⁵ purin nitrogen, Camerer-Arnstein.⁶ In order to make the analytical data clearer, they are expressed in terms of the nitrogen content of the substances determined and in terms of the percentile amounts they represent of the total nitrogen excreted each day.

2 Results—Adult dogs bear the effects of thyroidectomy remarkably well. Some of our animals lived comfortably for many months after the operation and without any obvious symptoms. This is to be explained by the fact that endocrine activity is probably lessened in the adult. Dr. F. M. Allen informs us that he has had similar experience with thyroidectomized dogs at the Rockefeller Institute. Had it been practical to use young puppies for such difficult experiments, it is possible that the metabolic changes would have been more marked.

1 Janney, N. W. *Jour Biol Chem*, 1915, **20**, 321.

2 Janney, N. W., and Isaacson, V. I. *The Blood Sugar in Thyroid and Other Endocrine Diseases*, *THE ARCHIVES INT MED*, this issue.

3 Van Slyke, D. D., and Cullen, G. E. *Jour Biol Chem*, 1914, **19**, 211.

4 Folin, O., and Morris, J. L. *Jour Biol Chem*, 1914, **17**, 469.

5 Benedict, S. R. *Jour Biol Chem*, 1914, **18**, 191.

6 Method of Camerer-Arnstein, "Analyse des Harns," Neubauer-Huppert, 1913, **2**, 941.

TABLE 1—DOG 1 NITROGEN PARTITION
BEFORE THYROIDECTOMY

Day	Wt, Kg	Glucose, Fed, Gm	Vol Urine, Cc	Total N, Gm	N per Kg	Urea N		NH ₃ N		Purin N		Creatin N		Creatinin N		Rest N	
						Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%
1	10.8		360	3.00	0.278												
2	10.6		370	2.58	0.243					0.013	0.50						
3	10.5		380	2.37	0.226					0.012	0.50						
4	10.4		400	2.33	0.226					0.011	0.48						
5	10.3	154.5	440	2.03	0.197	1.33	65	0.17	8	0.011	0.54	0.081	3.9	0.038	1.8	0.40	19
6	10.3	154.5	330	1.60	0.155	1.01	63	0.20	12	0.010	0.55	0.085	5.3	0.048	3.0	0.25	15
7	10.3	154.5	340	1.67	0.162	1.12	67	0.21	12	0.009	0.54	0.085	5.0	0.035	2.0	0.21	12
8	10.1		330	2.10	0.208	1.54	73	0.17	8	0.010	0.48	0.081	3.8	0.038	1.8	0.26	12
9	9.9		415	2.10	0.212	1.52	72	0.16	8	0.010	0.48	0.081	3.8	0.038	1.8	0.29	13

AFTER THYROIDECTOMY

1	12.2		600	1.65	0.136	1.16	70	0.16	9	0.006	0.36	0.101	6.1	0.015	0.9	0.21	13
2	11.8		540	1.96	0.166	1.39	73	0.17	8	0.003	0.15	0.106	5.4	0.014	0.7	0.30	12
3	11.7	175.5	210	1.91	0.163	1.23	64	0.18	9	0.004	0.22	0.110	5.7	0.021	1.1	0.36	20
4	11.7	175.5	200	1.65	0.141	1.07	65	0.21	12	0.006	0.36	0.119	7.2	0.020	1.2	0.23	14
5	11.7	175.5	260	1.69	0.145	0.99	60	0.22	13	0.008	0.48	0.126	7.4	0.014	0.8	0.37	18
6	11.7		430	2.07	0.177	1.58	76	0.14	7	0.006	0.29	0.106	5.1	0.035	1.7	0.20	10
7	11.5		440	2.07	0.180	1.61	77	0.13	6	0.004	0.19	0.106	5.1	0.035	1.7	0.21	10

TABLE 2—DOG 2 NITROGEN PARTITION
BEFORE THYROIDECTOMY

Day	Wt, Kg	Glucose, Fed, Gm	Vol Urine, Cc	Total N, Gm	N per Kg	Urea N		NH ₃ N		Purin N		Creatin N		Creatinin N		Rest N	
						Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%
1	17.6		535	3.03	0.172	2.27	74	0.21	7	0.021	0.69	0.21	6.9	0.026	0.85	0.29	9.5
2	17.3		575	3.11	0.180	2.44	78	0.23	7	0.012	0.38	0.22	7.0	0.038	1.22	0.17	5.4
3	16.6	249	450	3.12	0.188	1.83	58	0.30	9	0.030	0.96	0.23	7.3	0.016	0.51	0.71	22.7
4	16.6	249	345	2.47	0.148	1.71	69	0.24	9	0.026	0.75	0.18	7.2	0.038	1.13	0.28	11.3
5	16.6	249	510	2.55	0.154	1.79	70	0.24	9	0.020	0.79	0.18	7.0	0.038	1.46	0.28	10.9
6	16.5		770	3.14	0.190	2.54	80	0.21	8	0.020	0.65	0.20	6.3	0.022	0.70	0.30	4.7

AFTER THYROIDECTOMY

1	14.9		610	2.22	0.149	*				0.015	0.69	0.18	8				
2	14.7		610	2.27	0.154	1.63	72	0.317	14	0.006	0.26	0.18	8				
3	14.5	217.5	610	2.58	0.177	1.96	76	0.188	7	0.022	0.84	0.18	7	0.022	0.86	0.21	9
4	14.5	217.5	505	1.78	0.122	1.06	69	0.366	20	0.020	1.10	0.17	9	0.004	0.25	0.16	8
5	14.5	217.5	570	1.65	0.113	1.08	66	0.206	12	0.015	0.89	0.17	10	0.023	1.39	0.16	9
6	14.5		420	2.19	0.151	1.72	77	0.145	7	0.013	0.58	0.17	8	0.023	1.05	0.11	7

* Urea N + NH₃N = 1.85 gm = 83 per cent total N

TABLE 3—DOG 3 NITROGEN PARTITION
BEFORE THYROIDECTOMY

Day	Wt, Kg	Glucose, Fed, Gm	Vol Urine, Cc	Total N, Gm	N per Kg	Urea N		NH ₃ N		Purin N		Creatin N		Creatinin N		Rest N	
						Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%
1	7.5		325	2.17	0.289	1.71	79.0	0.096	4.45	0.011	0.507	0.063	3.25	0.036	1.66	0.248	11.4
2	7.4		305	2.13	0.288	1.73	81.1	0.101	4.76	0.012	0.563	0.063	3.24	0.035	1.64	0.183	8.6
3	7.2	103	265	1.82	0.253	1.19	65.2	0.092	5.12	0.011	0.604	0.071	3.90	0.037	2.03	0.419	23.0
4	7.2	103	250	1.43	0.199	0.77	53.9	0.166	11.6	0.009	0.629	0.063	4.82	0.037	2.59	0.393	27.8
5	7.2	103	240	1.43	0.199	0.79	55.0	0.152	10.6	0.009	0.629	0.063	4.82	0.018	1.26	0.392	27.4
6	7.1		400	1.62	0.228	1.21	74.8	0.138	8.49	0.004	0.247	0.063	4.20	0.015	0.93	0.173	10.7
7	6.9		250	1.63	0.236	1.21	74.4	0.100	6.16	0.003	0.491	0.063	4.23	0.022	1.41	0.220	13.5

AFTER THYROIDECTOMY

1	7.0		250	2.65	0.379	1.92	72.5	0.50	19.7	0.007	0.26	0.062	2.3	0.037	1.4	0.12	4.5
2	6.9		290	2.72	0.395	1.99	73.1	0.46	16.9	0.007	0.24	0.055	2.8	0.043	1.6	0.16	5.9
3	6.8		320	2.94	0.433	2.13	72.5	0.60	20.5	0.007	0.24	0.056	1.9	0.048	1.6	0.10	3.4
4	6.7	100.5	235	2.73	0.408												
5	6.7	100.5	225	2.07	0.369												
6	6.7	100.5	285	1.99	0.278												
7	6.55		210	2.13	0.325												
8	6.55		345	3.09	0.472												

TABLE 4—DOG 4 NITROGEN PARTITION
BEFORE THYROIDECTOMY

Day	Wt, Kg	Glucose, Fed, Gm	Vol Urine, Cc	Total N, Gm	N per Kg	Urea N		NH ₃ N		Purin N		Creatin N		Creatinin N		Rest N	
						Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%
1	6.3		235	1.95	0.309	1.62	83.0	0.079	4.07	0.008	0.41	0.060	3.0	0.026	1.3	0.157	8.0
2*	6.2		275	1.88	0.303												
3	6.0		235	1.60	0.267	1.32	82.5	0.053	3.23	0.006	0.37	0.060	3.7	0.026	1.6	0.135	8.4
4	5.9		230	1.65	0.280	1.35	83.8	0.051	3.06	0.007	0.42	0.060	3.6	0.030	1.8	0.121	7.4
5	5.8	87.0	220	1.35	0.233	0.90	66.3	0.090	6.66	0.010	0.74	0.057	4.2	0.025	2.5	0.262	19.2
6	5.7	85.5	115	1.16	0.203	0.75	64.6	0.078	6.71	0.006	0.51	0.060	5.1	0.044	3.7	0.222	19.1
7	5.7	85.5	205	1.28	0.224	0.82	64.0	0.090	7.03	0.008	0.67	0.060	4.7	0.036	2.8	0.266	20.4
8	5.6		225	1.23	0.220	†				0.009	0.73	0.056	4.5	0.029	2.3	0.156	12.7

AFTER THYROIDECTOMY

1	5.30		105	1.85	0.349	1.52	82.1	0.059	4.8	0.005	0.28	0.061	3.63	0.028	1.9	0.14	7.6
2	5.25		210	1.71	0.326	1.33	77.8	0.087	5.0	0.005	0.30	0.058	3.10	0.026	2.0	0.29	11.7
3	5.10		185	1.51	0.300	1.25	82.7	0.080	5.3	0.005	0.33	0.056	3.71	0.020	1.3	0.10	6.6
4	5.00		155	1.60	0.320	1.33	82.1	0.086	5.3	0.005	0.31	0.057	3.56	0.019	1.2	0.19	6.2
5*	4.95	73.0	155														
6	5.00	73.0	105	0.68	0.196												
7	5.00	73.0	170	0.93	0.186												
8	5.00		200	0.98	0.196												
9	4.95		255	1.43	0.287												

* Specimen contaminated with feces

† Urea N + NH₃N = 0.93 gm = 80 per cent total N

This must be borne in mind in interpreting the results. It is also to be remembered that it requires a certain length of time for the myxedematous condition to develop after thyroidectomy. The metabolic disturbances reported by us, observed as they were at most a few weeks after the operation, are probably to be regarded as incipient.

Weight. Three of the four dogs had lost weight at the time of the examination and one had gained. The primary loss of weight may be caused by defective tissue nutrition due to the failure of thyroid function. Later, obesity tends to develop.

Nitrogen. The nitrogen excretion showed an inconstant variation. In two dogs it was diminished, in Dog 3 distinctly increased, while in Dog 4 no definite change took place. A decrease in the nitrogen elimination after thyroidectomy has been recorded by others.⁷ Underhill and Hilditch⁸ observed no very definite change.

Urea and Ammonia Excretion. The urea and ammonia varied in general with the total nitrogen excretion. In estimating changes in the metabolism, the experimental days on which glucose was fed are omitted from this discussion, as sugar disturbs the equilibrium of the nitrogen metabolites in the urine. The ammonia-nitrogen curve parallels, as usual, the total nitrogen, except in the case of Dog 3, in which animal it was unusually increased after thyroidectomy.

Purins. Here the most striking changes were observed. In every instance the thyroidectomy was followed by a distinct diminution in the purins, as the average values in the accompanying tables demonstrate. These results appear to be the only ones recorded definitely indicating that the normal level of endogenous purin metabolism is maintained by the thyroid. The significance of this finding will be discussed later.

Creatinin. This remained practically uninfluenced by thyroidectomy except in Dog 1, in which it was somewhat increased. None of our work shows any definite influence of the thyroid on creatinin metabolism. The creatinin excretion showed its usual tendency to remain almost constant from day to day.

Creatin. This substance is usually present in dog urine, though abnormal in the urine of man. It showed fluctuations from zero in Dog 2 after the operation to an increase after thyroidectomy in Dog 4. Creatin excretion is subject to wide variations, due to different causes, which have been discussed previously by Shaffer.⁹ Such causes

⁷ Hunter, A. *Quart Jour Exper Physiol*, 1914, **8**, 21. Greenwald, I. *Biochem Ztschr*, 1913, **14**, 363.

⁸ Underhill, F. P., and Hilditch, W. W. *Am Jour Physiol*, 1909-1910, **25**, 66.

⁹ Shaffer, P. A. *Am Jour Physiol*, 1908, **23**, 1.

were evidently exerting their influence here. We were unable to detect any changes in the creatin metabolism definitely referable to thyroidectomy.

III METABOLISM IN EXPERIMENTAL HYPERTHYROIDISM

1 *Experimental Plan*—The effect of administering large amounts of thyroid substance on the urinary end-products of protein metabolism has been obscured in previous experiments through the introduction and consequent effect on the results of the protein, purin, etc., in the thyroid material ingested. To avoid this source of uncertainty we made use of a concentrated solution of the thyroid hormone isolated and kindly donated by Dr. E. C. Kendall of the Mayo Clinic. This was

TABLE 5—HORMONE EXPERIMENT

Day	Wt., Kg.	Glucose Fed, Gm.	Vol. Urine, Cc.	Total N, Gm.	N per Kg.	Urea N		NH ₃ N		Purin N		Creatinin N		Creatin N		Rest N		Special	
						Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Hormone In- jected, Cc.	Uri- nary Glu- cose, Gm.
1	14.5		550	3.39	0.234	2.61	77	0.33	10	0.0036	0.16	0.19	5.6	0.0	0.0	0.25	7.5		
2	14.8		720	3.28	0.222	2.57	78	0.26	8	0.0112	0.34	0.19	5.6	0.0	0.0	0.25	7.6		
3	14.4		610	3.36	0.233	2.79	83	0.20	6	0.0098	0.26	0.18	5.4	0.0	0.0	0.18	5.3		
4	14.1		820	4.75	0.337	4.18	88	0.25	6	0.0147	0.30	0.19	4.0	0.038	0.8	0.08	1.7	35	
5	13.5		510	5.52	0.409	4.54	82	0.30	5	0.0224	0.40	0.19	3.5	0.125	2.2	0.34	6.1	15	
6	13.2	198	330	4.82	0.365	4.04	83	0.29	6	0.0217	0.45	0.19	3.8	0.070	1.4	0.21	4.3	15	2.2
7	13.4	201	630	5.07	0.378	4.06	80	0.37	7	0.0310	0.61	0.19	3.8	0.166	3.2	0.25	4.9	15	Trace
8	13.0		850	7.26	0.558	5.70	78	0.71	10	0.0430	0.59	0.19	2.5	0.085	1.1	0.54	7.4		
9	12.6		520	6.28	0.498	4.63	73	0.85	13	0.0220	0.35	0.15	2.3	0.066	1.0	0.56	8.8		
10	12.3		440	6.31	0.513														

analyzed by us. The doses administered contained so little nitrogen that the results cannot be influenced as mentioned. That this hormone preparation was active is not to be doubted, for it exerted a therapeutic effect on a cretin, as will be reported later in an experimental study of thyroid therapy.

The scheme adopted was to determine the normal fasting metabolism of nitrogen, urea, ammonia, etc., of a dog, after which large doses of the sterile hormone were injected subcutaneously. The methods employed have been alluded to in Section 2. The first hormone injection consisted of 35 c.c., which amount was reduced thereafter, 15 c.c. of the hormone being given daily. One c.c. of this liquid contained 0.96 mg. iodine, equivalent to about 3 mg. hormone. No local necrosis or infection followed the hormone injections. The

metabolic procedure was otherwise exactly that employed in the thyroidectomy experiments, fasting being maintained throughout

2 Results—This experiment afforded highly instructive results. A relatively enormous amount of the thyroid hormone was suddenly thrown into the organism. There ensued a latent period lasting until the following day. This phenomenon has been observed by Kendall. Then the temperature rose. The dog's skin became reddened. Hyperexcitability to touch developed, muscle twitchings following the slightest stimulus, increased reflexes and a distinct fine tremor of the paws were present. No exophthalmos was observed. It may be remarked that exophthalmos is very rarely seen in such experiments. Thus, Lampe, Liesegang and Klose¹⁰ in their exhaustive monograph on exophthalmic goiter and experimental hyperthyroidism, report that they were able experimentally to produce protruding eyeballs only in certain degenerative strains of fox terriers. The clinical appearance of our animal was, with the exception noted, that of typical hyperthyroidism. After the hormone injections were discontinued, the symptoms gradually subsided.

Metabolism Before the injections were given the excretion of the urinary nitrogenous substances was quite normal and regular, but thereafter a veritable metabolic storm broke loose. The total nitrogen practically doubled in amount during the next few days and remained high even after the hormone administration had ceased. The amounts of urea, ammonia and purins became correspondingly elevated. It is a remarkable fact that the creatinin remained absolutely unresponsive to this tremendous stimulus, and maintained its unchanged level throughout the experiment. Creatin, although absent previous to the injection, appeared in the urine in considerable amounts. The significance of this phenomenon is probably as follows: the hormone evidently caused a large increase of tissue and muscular breakdown of which creatin excretion is an evidence, providing, as in this case, it has been previously absent from the urine. The purin excretion of hyperthyroidism is especially interesting in view of the fact that the thyroidectomy experiments demonstrated that the purin metabolism is at least partly controlled by the thyroid. The purin elimination enormously increased during the period of hyperthyroidism, indeed, to the extent of 300 per cent.

Previous observations on the effect on the urinary nitrogen metabolites following the administration of thyroid material are but fragmentary. Cramer and Krause¹¹ observed what must of course take

¹⁰ Lampe, E., Liesegang, R. E., and Klose, H. *Beitr. z. klin. Chir.*, 1912, **77**, 757.

¹¹ Cramer, W., and Krause, R. A. *Physiol. Soc. Proc.*, 1912, **23**, *Jour. Physiol.*, 1912, **44**, 2.

place, that when the total nitrogen is increased by feeding thyroid material, a corresponding rise in the urea elimination ensues. Creatin appeared in the urine of their patient.

The Protein Sparing Action of Carbohydrates in Athyroidism and Hyperthyroidism — In the foregoing experiments opportunity was afforded for testing an interesting hypothesis of special scientific interest. A recent research by us² has emphasized the important influence exerted by the thyroid gland on carbohydrate metabolism. Carbohydrates when taken into the body are known to limit protein breakdown. This process is most plausibly explained by the hypothesis that they thus "spare" protein by affording materials which are built up into protein, perhaps thus limiting tissue loss. The thyroid is now recognized as having a decided influence on the growth and nutrition of the tissues. If we then estimate the degree of protein-sparing by carbohydrate before and after thyroidectomy, we can determine whether this process is a function of the thyroid, consequently whether the thyroid possibly builds up the tissues by means of metabolic products of carbohydrates. The results of these experiments are quite negative. Glucose, as the protocols clearly show, spared usually as much protein before as after thyroidectomy. This action is therefore not controlled by the thyroid gland so far as is indicated by these experiments. This result has no special clinical significance. It only shows that in cretinism and myxedema the normal relationship of carbohydrate to protein metabolism is maintained.

Carbohydrate was also administered in the hyperthyroidism experiment. This was done in order to determine the effect of carbohydrate on the abnormally increased nitrogen metabolism observed in this condition. The protocol of this experiment shows no definite decrease in the total nitrogen and urea, and a decided increase in the purin excretion on the sugar days. During the following days all these substances were markedly increased. In interpreting these results one must bear in mind that during the injection days there was a tendency for a greater excretion of all the urinary substances examined as a result of the increasing toxic effect of the hormone. That this is true is demonstrated by a study of the purin elimination which was largely increased even on the sugar days. Former investigation has shown that the effect of sugar on the protein metabolism is limited to urea and ammonia. The purins remained unaffected by the ingested glucose and were consequently relatively augmented in percentage. The ammonia in our case was not depressed by the sugar ingested. In view of this evidence of increasing tissue breakdown, the failure of the total nitrogen and urea to be decreased by the sugar administration, is not surprising, for without it the nitrogen and urea would likely have been excreted in increased amounts. The experiment is then

rather to be accepted as indicating that glucose exerts its sparing effect on protein metabolism also in hyperthyroidism. This experiment would thus offer an explanation for the results obtained by us in other experiments, to be reported later, showing that exophthalmic goiter patients do best on a mixed diet containing large amounts of nonnitrogenous foods, as the toxic loss of protein is partially combated in this way. The question of diet in thyroid diseases will be discussed in detail in a later communication.

IV CLINICAL METABOLISM EXPERIMENTS

1 *Clinical Material*—The cases included in the present study will be reported in detail in the third of this series of articles and are therefore but briefly extracted here.

CASE 1—Typical Cretin, Y K., woman, aged 23, possessed the usual characteristics: short stature, pendulous abdomen, coarse skin, thickened nose and lips, defective teeth and nails, mental development, that of a child of 6 years. The patient, who remained in the metabolic ward for nearly a year, improved somewhat on thyroid treatment.

CASE 2—Exophthalmic goiter, A H., man, aged 30, history of great loss of weight, increasing weakness and nervousness. The patient showed emaciation, constant fine tremor of hands, muscle twitchings, moist skin, large struma, with loud systolic bruit, marked exophthalmos, Stelwagen's and von Graefe's sign present. Prolonged metabolic studies demonstrated that his general metabolism was markedly increased, for it was necessary for him to consume 60 calories per kilogram to maintain weight equilibrium.

2 *Experimental Plan*—Use was made of the advantages offered by a metabolism ward, special diet kitchen and nurses trained in metabolism work. The technic employed by us in metabolic examinations of patients has been previously described in various publications, and therefore scarcely requires a detailed presentation. The usual care was given to the weighing of the food and collection of the excreta. The patients had already undergone a careful training in the ward, where they had been for several months for other experimental purposes. The results may be therefore regarded as reliable. The diet was purin-free for one week prior to and during the examination, was weighed and consisted of the following articles: oatmeal, farina, rice, egg, corn, tomato, onions, bread, butter, crackers, milk, orange, prunes, pears.

Under these conditions nitrogen partitions as before were carried out on these patients with an idea of determining the influence of thyroid disease on the urinary nitrogen metabolites.

3 *Nitrogen Partition in Cretinism*—The total nitrogen of the diet, as the protocols show, about equals the output, so that little nitrogen was lost or retained. The nitrogen elimination was low, but this seems due rather to the low protein, high carbohydrate and fat diet which necessarily constitutes a purin-free régime, than to any inherent ten-

dency of the cretin to a low nitrogen excretion The urea, ammonia and creatinin showed normal variations Creatin was present, which is abnormal The purin nitrogen and phosphates ranged in the lower level of the normal excretion of these substances The purins averaged 0.119 gm daily Normal variations are 0.08 to 0.25 gm daily

Scholz¹² has previously studied the urine of cretins in an extensive research published in 1905 when, unfortunately, few of the analytic methods were very reliable This fact, together with the uncertain

TABLE 6—Y. K., CRETIN URINARY NITROGEN PARTITION

Date	Vol Urine, Cc	N Intake, Gm	Total N Gm	Urea N		NH ₃ N		Purin N		Creatinin N		Creatin N		Rest N		P ₂ O ₅ , Gm
				Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	
9/5	685	10.40	7.01	5.84	83.3	0.33	4.7	0.119	1.69	0.260	3.7	0.028	0.40	0.43	6.1	1.33
9/6	1,470	10.42	7.11	5.95	83.7	0.44	6.1	0.126	1.77	0.292	4.1	0.003	0.42	0.30	4.2	1.49
9/7	1,154	10.42	6.81	5.47	80.3	0.50	7.4	0.118	1.71	0.299	4.4	0.033	0.48	0.47	6.8	1.13
9/8	870	10.40	6.78	5.56	81.1	0.49	7.6	0.113	1.73	0.268	3.9	0.005	0.12	0.34	5.0	1.53
10/31	820	8.00	6.14							0.319	5.2	0.023	0.37			
11/1	800	8.04	7.04							0.319	4.5	0.023	0.33			
11/6	998	8.11	5.51							0.318	5.8	0.024	0.44			

TABLE 7—J. H. EXOPHTHALMIC GOITER URINARY NITROGEN PARTITION

Date	Vol Urine, Cc	N Intake, Gm	Total N Gm	Urea N		NH ₃ N		Purin N		Creatinin N		Creatin N		Rest N		P ₂ O ₅ , Gm
				Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	
9/5	1,320	14.94	9.84	7.40	75.0	0.85	8.6	0.191	1.9	0.354	3.6	0.041	0.41	1.01	10.0	2.25
9/6	1,175	14.98	9.92	7.46	75.2	0.78	7.9	0.187	1.9	0.343	3.5	0.024	0.24	1.13	11.4	2.54
9/7	1,245	14.94	9.80	7.35	74.1	0.90	8.3	0.162	1.6	0.352	3.6	0.0	0.0	1.04	10.6	2.35
10/31	1,300	11.68	7.96					0.123	1.5	0.362	4.5	0.023	0.30			
11/1	1,500	11.50	7.99					0.086	1.1	0.323	4.0	0.023	0.29			
11/6	1,410	11.85	9.76					0.040	0.5	0.328	3.4	0.047	0.48			

activity of the thyroid preparations used at the time, would adequately account for the considerable variations shown by his results His work, however, indicated that in the cretin, uric acid and phosphates and creatinin, the last in variance with our results, were eliminated in decreased amounts McCrudden¹³ found creatin present in the urine of a cretin, also in cases of infantilism and achondroplasia Greenwald¹⁴ confirmed certain of these results

12 Scholz, W. Ztschr. f. exper. Path. u. Therap., 1905-1906, 2, 271
13 McCrudden, F. H. Jour. Exper. Med., 1912, 15, 467
14 Greenwald, I. THE ARCHIVES INT. MED., 1914, 14, 374

4 *Nitrogen Partition in Exophthalmic Goiter*—In these experiments the total nitrogen in the urine was found to about equal the intake. Protein metabolism in this case was undoubtedly increased, as a long series of later observations not appearing in this article, amply demonstrated. The urea nitrogen was normal in percentile relation to the total nitrogen. The ammonia tended to be high. In three of the four partition days, creatin was present in the urine. That creatin was consistently excreted in this case is shown by subsequent examinations as follows: Oct 31, 1916, creatin 0.023 gm, Nov 1, 1916, creatin 0.023 gm, Nov 6, 1916, creatin 0.047 gm. The purin nitrogen and phosphate excretion were at the upper level of normal. In view of the striking increase of purin metabolism found by us in experimental hyperthyroidism, it is more likely that the purins will, on examination of a series of cases of uncomplicated hyperthyroidism, be likewise found increased rather than decreased, as reported by Falta and Zehner¹⁵. The creatinin in our case was a little low. Forschbach¹⁶ has reported the same observation. As creatinin remains unaffected in experimental hyperthyroidism (see the foregoing), it is probable that its increase here is to be explained by the fact that sometimes the appearance of creatin is accompanied by a diminution of the amount of creatinin eliminated, the creatin being apparently formed at the expense of the creatinin. Excretion of creatin in exophthalmic goiter has been studied by Shaffer⁹ and has been observed by others.

V DISCUSSION AND CONCLUSIONS

We may now endeavor to piece together the results of the nitrogen partitions in the various experiments described, and draw from them what general conclusions are justified with regard to the urinary nitrogenous substances in our studies. No selective action of the thyroid was observed on urea and ammonia. The percentages of these substances remained within normal limits. The amounts present varied with the total nitrogen, in the usual manner. Our experimental studies definitely demonstrate that the thyroid exerts an influence on purin metabolism, as we observed both a decrease in the urinary purins after thyroidectomy and a marked increase in experimental hyperthyroidism, also a tendency to a low purin excretion in the cretin and a high excretion in a case of exophthalmic goiter. The clinical observations thus tend to confirm the experimental findings but should be extended before conclusions are justified.

The behavior of the purin metabolism in hypophysial disease seems to be analogous to that in thyroid disease. In the few cases investi-

15 Falta, W. *Die Erkrankungen der Blutdrüsen*, Berlin, 1913, p. 66.

16 Forschbach. *Arch f exper Path u Pharmakol*, 1907, 63, 113.

gated, the endogenous purin excretion is reported high in acromegaly by Falta and Nowaczynski¹⁷ The same investigators found a decreased uric acid elimination in hypopituitarism (Frohlich's syndrome) The observation that the thyroid exerts an influence over purin metabolism analogous to the effect of the hypophysis is important, and a further illustration of the fact which is becoming more and more apparent, namely, that several of the endocrine organs may exert very similar influences on the metabolic processes

With regard to clinical applications, it might seem, in view of these results, justifiable to seek the cause of gout in an endocrine disturbance So far, however, as the thyroid and hypophysis are concerned clinical observations do not support a relation of diseases of these organs to gout One might likewise feel inclined to administer thyroid or pituitary tablets to gouty patients in the hope of stimulating the excretion of the purins According to our views, however, this would scarcely be advisable, at least in the case of thyroid, for it is probable that the excretion of purins is increased only as the result of a toxic effect of large doses of thyroid on the protein of the tissues (compare hormone experiment)

Our studies emphasize the independence of the creatinin metabolism from thyroid influence Creatinin was not increased in the urine even when large amounts of body tissue were being broken down in experimental hyperthyroidism This would seem to indicate that creatinin is not a direct product of protein catabolism With regard to creatin, it is indeed strange that a product which is chemically merely hydrated creatinin should appear in the urine while the creatinin undergoes but little change This apparent independence of creatin from creatinin metabolism is striking A number of previous observations have, however, shown this to occur under other circumstances

In the thyroidectomy experiments the creatin determinations are not very valuable, as this substance is usually present in normal dog urine However, the fact that it is found in cretinism and exophthalmic goiter deserves consideration Creatin is usually excreted when masses of body tissue are being broken down, such as takes place in severe febrile conditions Such is, however not the case in cretinism Its appearance in this condition is probably due to a disturbance in the normal synthetic metabolic processes which take place by means of intermediary chemical reactions which are as yet little understood but may be disturbances in the metabolism of carbohydrates The creatinuria of exophthalmic goiter seems more easy of comprehension than that of cretinism, for in exophthalmic goiter there is frequently a toxic breakdown of body tissue which may be held to account for the appearance of creatin

17 Falta, W Ductless Glandular Diseases Philadelphia, 1916, p 263

The present experiments do not support the view that any marked diminution of nitrogen excretion follows thyroidectomy in animals (see the foregoing) Nor was the nitrogen output particularly low in the cretin There are, moreover, reasons to believe that the decrease in the protom breakdown, observed by others in the cretin metabolism, is due rather to an inability for growth and repair of tissue to take place These views will be more fully developed in the next article of this series

We wish to acknowledge the excellent assistance rendered by Miss Maude Hays in the dietetic and analytic work of this research

III STUDIES IN THYROID THERAPY

THE EFFECTS OF THE THYROID HORMONE AS DETERMINED BY A CLINICAL METABOLIC AND DIETETIC INVESTIGATION NEW POINTS OF VIEW ON THYROID FUNCTION IN HEALTH AND DISEASE *

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I INTRODUCTION AND SUMMARY

Of all attempts at organotherapy, the most brilliant results have been obtained with thyroid preparations. This fact lends especial interest to the isolation of the active substance of the thyroid, as well as its employment in the treatment of disease. Some time ago a crystalline body containing upwards of 60 per cent of iodine was prepared from the thyroid by Kendall of the Mayo Clinic. Observations made on cretins and myxedema patients justify the view that this substance is to be regarded as a hormone having the functions ascribed to the thyroid. Some time back Dr Kendall generously presented me with a quantity of this material for independent study.

The present article describes therapeutic experiments with this thyroid preparation, the effect of thyroid administration on metabolism, and of diet in thyroid disease. In view of the importance of a thorough study of the thyroid hormone, it was decided to follow its action with the aid of (1) concomitant metabolic investigations, (2) strict control of the dietary régime by specially analyzed and weighed diets, (3) prolonged periods of observation (varying from three to thirty-seven weeks), (4) parallel observations of the effect of other thyroid preparations, (5) series of normal control cases.

On account of the unusual amount of special food preparation, special nursing, and analytic work required, only a limited number of cases could be included. All deductions made in this article are therefore subject to this criticism. It is, however, believed that less material thoroughly studied is of greater value than a larger number of cases which have been merely subjected to the usual clinical methods of control.

In order to establish a definite gauge of the activity of the thyroid preparations given it was determined to follow the effects on the pro-

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* From the Montefiore Hospital, New York City. A preliminary report of this research was read before the Academy of Medicine, Section of Internal Medicine, New York, December, 1916.

tein metabolism over continued periods, with estimation of the nitrogen intake, output and balance. It was found that the nitrogen balance is a rather delicate measure of the action of the hormone. *The results are of unusual interest, for they very definitely indicate that a gain, not a loss, of nitrogen is a result of the therapeutic action of the thyroid, and vice versa, that a loss of nitrogen, that is, protein, is due to a toxic action of the gland*

The thyroid hormone was found to have a definite therapeutic effect in cretinism, improvement in the clinical symptoms and a gain in nitrogen retention resulting. The optimal daily dose was found to be 0.25 mg hormone iodin, representing approximately 0.75 mg hormone, and corresponding to 4 grains of thyroid tablets. It could thus be demonstrated that usually too great an amount of thyroid is prescribed in hypothyroidism. The use of the thyroid hormone in minimal doses, that is, 0.02 to 0.06 mg hormone iodin daily in Graves' disease, was followed by increased retention of nitrogen but by no certainly established therapeutic effect. The thyroid treatment of obesity depends on a toxic effect, as it is accompanied by nitrogen loss. It should therefore be discouraged.

The effect of diet in thyroid disease was also critically reviewed and investigated. In cretinism, as in normal individuals, an evenly balanced protein, fat and carbohydrate diet is followed by the best results. In exophthalmic goiter, as has been previously observed, very greatly increased amounts of food are necessary in order to combat the toxic combustion. A high caloric mixed diet was found to be the diet of choice in this condition. The relation of diet to the therapeutic action of thyroid preparations was also investigated.

From this and other studies¹ of the thyroid problem, certain changes in point of view toward thyroid function in thyroid diseases are developed and included in the general discussion. They comprise (1) the conception of the anabolic and therapeutic action in contradistinction to the catabolic or toxic action of the gland or its preparations, (2) a discussion of metabolism in hypothyroidism, (3) the hormone hypothesis of the pathogenesis of exophthalmic goiter.

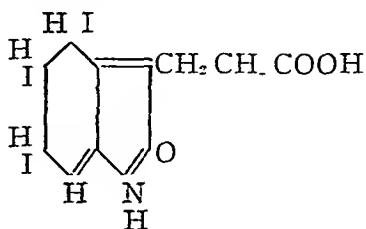
II THE PREPARATION AND PROPERTIES OF THE THYROID HORMONE

For the isolation of the thyroid hormone the profession is indebted to Dr. E. C. Kendall.² The principles of its separation are hydrolysis of thyroids by sodium hydroxid into α -iodin proteins, insoluble in

1 Janney, N. W., and Isaacson, V. I. The Effect of Thyroidectomy and Thyroid Diseases on the Protein Metabolites, and The Blood Sugar in Thyroid and Other Endocrine Diseases, in this issue.

2 Kendall, E. C. Fed. Am. Soc. Exper. Biol., New York, Dec. 30, 1916, Collected Papers, Mayo Clinic, 1916, Jour. Biol. Chem., 1915, **20**, 501.

acids, and *b*-iodin proteins soluble in acids. In the *a*-iodin fraction is contained 2 to 50 per cent of the total iodin in the gland. This fraction alone seems physiologically active. From it was later isolated a body crystallizing in microscopic sheaths containing 65 per cent iodine, of the high atomic weight 586, having the formula $C_{11}H_{10}O_3NI_3$, being structurally according to Kendall tentatively as follows



Here it may be said that this compound still awaits satisfactory identification by publication of the detailed methods of isolation, elemental analyses, and complete proof of the correctness of the structural formula by synthesis or otherwise, and finally confirmation of these results. Before this crystalline substance can be accepted as the thyroid hormone, however, the main question to be answered is its physiologic activity. This point has been answered by work done at the Mayo Clinic, which showed not only that toxic symptoms produced by the thyroid gland or its extracts are also produced by this isolated substance, but also that it causes cretins to grow and return to their normal condition. The present article goes far toward confirming these results. Apparently but one hormone is present in the thyroid.

A considerable difference in the action of the hormone on dog and man was found by Kendall to exist. In the canine 1 mg per kilogram body weight is required for toxicity while $\frac{1}{75}$ to $\frac{1}{25}$ of 1 mg per kilogram body weight per day has caused toxic symptoms in man. The toxic period is preceded by a latent period of one or more days and includes increased pulse rate, irritability to touch, fine tremor, increased appetite, then nausea and diarrhea.

The production of the thyroid hormone has not as yet attained commercial proportions. The largest amount as yet obtained is 20 gm.³

III EXPERIMENTAL TECHNIC

The general methods employed here have been previously alluded to in various articles by the author and his co-workers.¹ The effects of extraneous influences on the patients were avoided by having them occupy separate rooms in a metabolic ward one or two weeks previous to and during the examination, and by permitting no other treatment in addition to thyroid therapy except prescribed periods of rest, fresh air and walking. Special nurses trained in this work were employed

³ Kendall, E. C. Verbal communication.

and the patients remained under constant control day and night. Previous to the experimental periods, each patient was put through a preliminary training in keeping faithfully to the prescribed weighed diet, and in accurate collection of urine and feces. With the help of properly trained nurses, we have found no difficulty in collecting an exact twenty-four-hour specimen of urine from even female patients over long periods of time. The regularity of the values recorded in the protocols is the best proof which can be afforded of this statement. The cases here reported were selected from among patients taken into the ward but not found adaptable to exact study.

The dietaries employed were calculated on the basis of Meeh's weight-height formula for the basal requirement, allowance being made for sex, age, activity and the elevation or depression of the total metabolism in thyroid conditions. Practically every article of food was sampled and analyzed for nitrogen, and the articles in the diet selected as simply as possible to avoid all possible errors in this regard. In spite of this, experience has shown that it is very difficult to attain absolute exactness. It must be remembered, however, that it is the relative differences rather than the absolute values that are of importance in these metabolic experiments. It seems superfluous to enumerate the various constituents of the dietaries.

The Nitrogen Balance — In obtaining this value, the various amounts of nitrogen in the separate foods were calculated, and the total nitrogenous intake of the day balanced against the sum of the nitrogen excreted in the urine and feces. The twenty-four-hour urine was regularly collected. For greater accuracy, the feces were segregated usually at weekly intervals, the weekly amount dried, and the nitrogen estimated. Although regularly made, slight importance was attached to the daily balances. On account of the large number of daily balances (500 to 600) the daily protocols reproduced in this article are limited to a few specimen periods. Generally weekly periods are represented giving the average value of the nitrogen of the food, urine, feces and balance figures.

The hormone was preserved in sterile neutral solution. It was conveniently administered in the form of weak standard solutions, 1 c.c. containing 0.01 or 0.001 mg. iodine. The hormone preparation sent us by Dr. Kendall contained 32 per cent iodine, so that the actual amount of hormone given was about three times that of the iodine. Although our preparation contained other substances than the hormone, which accounts for its lower iodine content, they proved to be physiologically inactive, both in the experience of Dr. Kendall and ourselves, and do not, therefore, influence the results. We have used the iodine content of the hormone as a

standard for dosage throughout the present paper and refer, therefore, to the hormone iodin or H I, rather than to the hormone itself

We have found it convenient to administer the hormone by mouth In the form in which it is employed by us, it is tasteless Its therapeutic action is not affected by its passage through the gastro-intestinal tract For this statement we have the evidence of accumulated clinical experience, as the oral method of thyroid medication has been used with good results

As previously noted by Kendall, our hormone preparation though remaining active over many months, eventually suffered deterioration This suggests that even excellently prepared thyroid tablets, whose effect depends on the hormone contained in them, should be expected to lose their effect in time This fact is confirmed by clinical experience

IV CONTROL EXPERIMENTS

As therapeutic effects are obtained by small doses of thyroid, it was decided to endeavor to detect metabolic and other changes by this means, rather than to follow the action of markedly toxic doses as had already been frequently done by other investigators Endocrine activity is greater in the young, therefore two of the selected three cases were children

CASE 1—S M, girl, aged 12 years Diagnosis, fully compensated endocarditis This patient's requirement was 1,887 calories, but throughout the experiments diets supplying approximately 2,100 calories were given The purpose of this increase was to exclude the effects of an overrestricted diet on the nitrogen balance, it being known that under these circumstances nitrogen may be lost due to tissue combustion for fuel purposes That an adequate diet was given is shown by the gain in weight, which amounted to 3 pounds and 4 ounces during the two months of the experiment

TABLE 1—S M CONTROL CASE

Period	Date	Change in Weight, lb oz.	N Intake Gm	N in Urine, Gm	N in Feces, Gm	N Balance, Gm	Medication	Diet			
								Prot, Gm	Fat, Gm	Carb., Gm	Cal
1	7/ 6-11*	— 2	3 23	2 33	1 16	—0.21	None	20	53	268 (7/6-19)	2,100
2	7/13-19†	— 4	3 23	1 98	1 37	—0.07	0.33 gm gland				
3	7/23-29	+1 2	12 04	9 15	0 95	—1.93	None	77	87	245 (7/20-9/8)	2 111
4	7/30-8/5	— 12	11 94	8 57	0 85	—2.62	None				
5	8/ 6-12	+ 4	12 04	8 85	0 92	—2.28	0.33 gm gland				
6	8/13-19	+ 2	11 92	9 33	1 10	—1.49	0.33 gm gland				
7	8/20-26	+ 10	12 15	9 19	1 56	—1.41	0.005 mg H I				
8	8/27-9/8	— 12	12 19	8 81	0 85	—2.52	None				

* July 12, balance omitted Diet unchanged

† July 20-23, balance omitted to allow change of diet to have its effect

During Periods 1 and 2, a diet very low in nitrogen was given. After having been a week on the diet, on which the patient lost weight and showed a negative nitrogen balance, it was decided to determine the effect of a minute dose of thyroid (0.38 gm gland). Practically no clinical or metabolic changes took place.

The diet was then altered to a normally mixed diet. After having observed a two weeks' balance without medication, the same amount of fresh gland was again administered. During Periods 5 and 6, a depression of the nitrogen balance as compared to that of the foreperiods was noted, also a tendency for less weight to be gained. In Period 7, during which 0.005 mg hormone iodine was prescribed, the nitrogen balance remained low, although a tendency to gain weight was resumed. After stopping the medication in Period 8, a higher plus balance and increased weight resulted. It will be noted that during the medication Periods 2, 6 and 7, increased amounts of nitrogen were lost in the stools, which loss ceased when the thyroid ingestion was stopped. The clinical condition remained unchanged throughout.

CASE 2—A S, girl, aged 12 years. Diagnosis, chronic endocarditis, fully compensated. This patient's requirement was 1,738 calories. She remained on a normal mixed diet supplying 2,088 calories during the entire period of examination.

TABLE 2—A S CONTROL CASE

Period	Date	Change in Weight, lb oz	N Intake, Gm	N in Urine, Gm	N in Feces, Gm	N Balance, Gm	Medication	Diet			
								Prot, Gm	Fat, Gm	Carb, Gm	Cal
1	4/10-17	+1 12	10.53	7.08	1.05	+2.40	None	62	56	197	2,088 (Diet throughout)
2	4/18-24	— 2	10.52	7.22	1.13	+2.17	0.32 gm gland				
3	4/25-5/1	+ 12	10.54	7.38	1.17	+1.99	0.32 gm gland†				
4	5/ 2-8*	+1 4	10.54	7.70	1.23	+1.60	0.16 gm gland‡				
5	5/16-22	+ 12	10.54	8.15	1.47	+0.91	34 mg tablet§				
6	5/23-26	+ 10	10.54	8.06	1.46	+1.02	17 mg tablet				
7	5/27-29			7.54	1.29	+1.71	None				
8	5/30-6/5	+ 8	10.54	7.89	1.20	+1.43	85 mg tablet				

* May 9-15 omitted. Diet unchanged. Error in collection.

† Medication stopped last two days.

‡ On 1st day, 34 mg tablet given.

§ On May 19 changed to 17 mg tablet.

An inspection of the protocols confirms the results obtained in the previous experiment. The same amount of fresh thyroid per kilogram of body-weight as was given S. M. caused an increase in the urinary as well as the fecal nitrogen output and a consequent decrease in the balance. In Period 3 slight tachycardia developed, the thyroid was therefore discontinued for two days. One half the preceding dose was then administered. No clinical toxic symptoms were now observable but the nitrogen balance continued to decline. In Periods 5 and 6, Armour's thyroid tablets containing 0.2 per cent iodine were given. The result was a further decrease in the nitrogen balance. When the thyroid medication was stopped for two days (Period 7) an increase in the balance occurred. The loss in the balance was resumed on the administration of 85 mg tablet in Period 8. Aside from the toxicity exhibited in Period 3, the child's condition remained excellent throughout.

CASE 3—B. C., woman, aged 25 years. Diagnosis, mild neurasthenia. Requirement, 1,645 calories. The diet supplied 1,545 calories and a sufficiency

of protein The patient lost weight, which may have been due to the fact that her actual requirement was greater than the one calculated, due to greater muscular activity induced by her nervousness Although there is no definite relationship between the loss of weight, in the case of this patient, and the thyroid administered, there is observable a distinct effect of the medication on the nitrogen balance In Periods 2 and 3 when hormone iodin in doses of 0.01 and 0.02 mg, respectively, were given, it is seen that a very markedly depressant effect on the nitrogen balance ensued, the lowest balance being obtained when most hormone was ingested In Period 4 when treatment was stopped, a tendency to a return to a higher balance was exhibited The patient's clinical condition remained unchanged during the entire course of the experiment

Conclusions from the Control Experiments—The results of this series indicate that the normal organism is more sensitive to minute doses of thyroid than had been previously supposed The earliest observable effect is a tendency for a positive nitrogen balance to diminish, this condition being sometimes accompanied by a loss of weight The same effects were observed both on diets containing normal and decreased amounts of nitrogen, in the latter case the results being naturally less marked

TABLE 3—B C CONTROL CASE

Period	Date	Change in Weight, lb oz	N Intake, Gm	N in Urine, Gm	N in Feces, Gm	N Balance, Gm	Medication	Diet			
								Prot, Gm	Fat, Gm	Carb., Gm	Cal
1	9/16-22	-1 2	8.53	6.71	0.41	+1.42	0	53	55	197	1,545
2	9/23-29	+ 2	8.53	7.35	0.57	+0.61	0.01 mg H I	(Diet throughout)			
3	9/30-10/6	- 14	8.56	7.36	1.04	+0.16	0.02 mg H I				
4	10/7-13	-1 8	8.57	6.94	1.04	+0.59	0				

A decreased retention of nitrogen was obtained with fresh gland, Armour's tablets, and Kendall's hormone, when given to individuals with normally functioning thyroids The deduction may therefore be drawn that the hormone is the active principle of the thyroid gland as it produces results identical with those obtained with the other preparations Kendall's statements with regard to the specific action of the thyroid hormone receives, therefore, new corroboration

Since a decreased nitrogen retention is observable in normal cases when thyroid preparations are administered, the inference may be drawn that in the case of normally functioning thyroids, the smallest amounts of hormone added from without tend to cause nitrogen loss Reasons for regarding this effect as a toxic indication will be given later in the article Identical doses of the hormone have a very different action in thyroid diseases as the following sections demonstrate

V CRETIN EXPERIMENTS

CASE 4—*Abstract of Case History*—Y K, woman, aged 25 years, Austrian Jewess. Diagnosis, sporadic cretinism. From birth, growth and intelligence were markedly subnormal. The large head and abdomen receded somewhat in size on beginning menstruating at the thirteenth year, dysmenorrhea and irregularity since, patient unable to learn at school, is both irritable and stupid.

Examination—Typical cretin. Height, 4 feet 5½ inches, short, thick-set trunk, short extremities, intelligence that of child of 4 years, skin coarse and covered with coarse hair, speech guttural, vision defective, bulging forehead, saddle nose, teeth poorly calcified, tongue voluminous, large cystic goiter, right lobe larger, systolic bruit, circumference of neck, 15½ inches, heart not enlarged, functional murmurs at times, abdomen pendulous and fat, palms of hands and soles of feet padded, genitalia normal, pulse regular, 80 to 100 in rate, temperature 99 to 99.5, blood pressure normal, Wassermann test negative. Roentgen examination showed underdevelopment of anterior skull and face bones, absence of frontal sinuses, thickened occipital bones, thinned maxilla. Persistence of epiphyseal lines of long bones.

Experimental—In the experiments on this patient not only the effect of administering various thyroid preparations in varying doses, but also the effect of diet was studied. The latter will be treated in a special section. During the first nine experimental periods the patient remained on a fixed weighed diet, containing the food classes in the usual relations and supplying 2,192 calories, or 50 calories per kilogram.

During Periods 2 and 3 the effect of the daily administration of 0.5 gm fresh gland was studied. The patient, who had not received thyroid medication for a long time, became appreciably brighter mentally and ceased to complain of headache, with which she was constantly troubled when not treated with proper doses of thyroid. The effect on the nitrogen balance was striking, for though positive in the foreperiods, it increased by nearly 100 per cent. The weight also increased.

During Period 4, treatment was stopped. The balance remained high, however. This was probably due to the two weeks' previous treatment. In Periods 5 and 6 the fresh gland treatment was resumed. A decreased nitrogen balance was observed, which was, however, at a higher level than in Period 1. Clinically, the patient's condition improved steadily, her skin became clearer and her intelligence brighter.

The differences in the effect of the fresh gland is probably to be ascribed to the greatly varying iodine content of the thyroids of different animals. According to Seidell and Fenger⁴ the iodine of the dried gland ranges from 0.04 to 0.33 per cent, undergoing seasonal and other variations. Differences in effect when identical doses were prescribed may be observed in the protocols. During Periods 7, 8 and 9, 50 mg of thyroid tablets were prescribed. This dose was calculated to contain 0.05 mg hormone iodine. That the amount was inadequate could be demonstrated from the fact that the cretin's headache returned, her clinical condition generally was not as good, and her metabolism was not as favorably influenced.

Low Protein Periods—The cretin next went on a low protein, high carbohydrate diet, supplying about the same number of calories as previously. On this diet she evidently suffered from nitrogen deficiency and lost weight (Period 10). The administration of 0.5 gm of fresh gland (Periods 11 and 12) did not benefit her markedly, although a tendency for a slightly increased balance was observable. From these periods the important deduction can be drawn that *a correct dietary is necessary to obtain a beneficial effect of thyroid treatment, also that the effect of the thyroid treatment is accomplished through its influence in increasing the power to assimilate a proper diet.* The results

4 Seidell, A., and Fenger, F. Jour Biol Chem, 1912-1913, **13**, 517

here obtained do not substantiate the generally quoted view that cretins require less nitrogen for maintenance than do normal individuals

High Protein Periods—During the next six periods (13 to 18, inclusive) the patient was given a high protein diet corresponding calorically very closely to the diets previously given. The initial gain in weight and nitrogen on this régime (Period 13) was probably due to compensatory effects for the low protein of the preceding diet. In the next three periods (14, 15 and 16)

TABLE 4—Y. K. CRETIN

Period	Date*	Change in Weight, lb. oz.	N Intake Gm	N in Urine, Gm	N in Feces, Gm	N Balance, Gm	Medication	Diet			
								Prot, Gm	Fat, Gm	Carb., Gm	Cal
1	2/13-19	-1 6	10.54	8.20	0.96	-1.32	0	67	56	242	2,102
2	3/23-4/3	- 6	10.54	7.05	1.05	-2.43	0.5 gm gland	(5/13-5/27)			
3	4/4-10	- 4	10.54	6.95	0.97	-2.62	0.5 gm gland				
4	4/16-22	- 6	10.54	7.15	1.05	-2.34	0				
5	4/23-29	- 10	10.54	7.19	1.23	-2.12	0.5 gm gland				
6	4/30-5/6	- 12	10.54	7.25	1.61	-1.68	0.5 gm gland				
7	5/7-13	= 0	10.54	7.35	1.11	-2.07	50 mg tablet				
8	5/14-20	- 8	10.54	7.65	1.10	-1.78	50 mg tablet				
9	5/21-27	- 2	10.54	8.13	1.12	-1.29	50 mg tablet				
10	6/14-20	- 8	4.81	3.49	0.82	-0.01	0	87	50	220	1,866
11	6/28-4	= 0	4.81	2.91	0.72	-0.67	0.5 gm gland	(6/4-7/11)			
12	7/5-11	-1	4.81	3.16	0.77	-0.88	0.5 gm gland				
13	7/17-23	-1	16.06	9.65	2.21	-4.26	0	101	95	249	2,125
14	7/24-30	= 0	15.95	11.44	1.61	-2.89	0	(7/12-8/25)			
15	8/31-9/6	- 2	16.20	11.40	1.60	-3.02	0				
16	8/7-9	- 4	16.18	11.31	1.07	-3.89	0				
17	8/10-15	- 2	16.18	11.33	1.46	-3.26	0.48 mg H I				
18	8/21-25	.	15.26	11.68	1.74	-1.54	0.25 mg H I				
19	9/5-11	-2	10.46	7.03	1.04	-2.25	0	As in Periods 1-9			
20	9/26-10/2	- 14	10.45	7.34	1.04	-2.07	0.5 gm gland				
21	10/6-10	-2 14	7.96	7.57	0.64	-0.13	0	50	53	189	1,409
22	10/18-24	- 2	8.02	6.01	0.69	-1.32	0.25 mg H I				
23	10/25-31	- 12	8.04	6.28	0.76	-1.00	0				

* Although the balance was omitted on the following dates the diet remained the same as in the preceding period: 3/20-27, 4/11-15, 6/21-28, 8/16-21, 9/25-10/2, 10/11-18.

On the following dates, 5/28-6/14, 7/12-17, 8/26-9/5, 10/3-6, the balance was omitted to allow the change of diet to have its effect.

less weight and nitrogen were gained. The patient who had now gone without thyroid medication for a month had experienced a return of her characteristic headaches. Her skin color and texture as well as her mentality, which had been improving under treatment, now failed to undergo further betterment.

After this comprehensive preliminary study, the first trial with the thyroid hormone was made. A daily dose of 0.48 mg hormone iodine was given by mouth for six days (Period 17). This dose was evidently too large for

mental excitability, tachycardia and precordial oppression soon developed. This toxic effect is reflected in the failure to gain nitrogen. An interval of four days, in which no thyroid was given, was not sufficient for the clinical toxicity to subside, for a reduction of the hormone dosage in Period 18 failed to influence favorably either the clinical symptoms or to prevent a further loss of nitrogen. The nitrogen balance for this period is consequently low. During the course of these investigations we have frequently noted that the toxic symptoms due to an overdose of thyroid may endure for some time after the medication has been stopped.

In spite of the pauses made in her treatment as well as the slight evidences of toxicity at times caused by overdosage, the cretin's general condition had considerably improved as compared to that of six months previously (Period 1). We therefore determined to have the patient return to her original diet in order to discover whether the clinical improvement was not reflected in her general metabolism. This was accordingly done (Periods 19 and 20). The results proved the correctness of our supposition. It was found that on the liberal mixed diet the patient gained 2 pounds in weight, though fat did not noticeably increase, and the nitrogen balance rose nearly to the height attained when most favorably influenced by the thyroid medication one-half a year before. In Period 20, with 0.5 gm fresh gland, the nitrogen balance exhibited a tendency to fall rather than rise. For this result we have no satisfactory explanation, unless it be that temporarily no additional hormone was required, the dose here given acting in excess as in normal individuals.

The last series of experiments (Periods 21, 22 and 23) were planned to trace the effect of the hormone when the patient was on a bare maintenance mixed diet. During the preliminary period (21), the cretin lost 2 pounds and 14 ounces and the nitrogen balance approached zero. When 0.25 mg hormone iodine was administered, weight ceased to be lost and the nitrogen balance jumped to plus 1.32 gm daily, which is ten times that of the previous week. The clinical symptoms again confirmed these signs of improvement. When the hormone was stopped (Period 23) weight was again lost and the nitrogen balance tended to decrease. *These periods demonstrate in the most convincing fashion the therapeutic effect of the thyroid hormone.*

The effect of hormone treatment is well exemplified in the blood picture. On Aug 17, 1916, the hemoglobin was 70 per cent, the erythrocytes 4,000,000, while on Nov 17, 1916, the hemoglobin was 85 per cent, and the red count 4,800,000. The differential counts are likewise of interest, the lymphocytes decreasing during the same interval from 46 to 33 per cent. The mononuclear cells (4 to 12.5 per cent) failed to show a corresponding decrease. Similar blood changes in myxedema and cretin cases undergoing treatment have been previously observed.

The weight changes in a cretin during a course of treatment are of interest. The resumption of growth is of course accompanied by a general increase of body weight. On the other hand, the amount of fatty tissue of the body usually decreases. There is thus exhibited a certain tendency to counterbalance gain with loss of weight, which must be taken into account. On beginning our observations, the patient's naked weight was 96 pounds (March 13, 1916), she reached a maximum weight of 106 pounds on Oct 2, 1916, and declined to 99 pounds 4 ounces on Jan 20, 1917, with the restricted diet used during this period. In our case, in spite of intermittent treatment, the increase of weight is thus seen to be quite large, amounting to 10 pounds, or 10 per cent of the total. In view of the general improve-

ment, it can be considered as real growth, although the height was not affected, as was to be expected in view of the mature age of the patient.

Finally, the effect of treatment was also seen on the metabolism. Hypothyroid conditions are characterized by a delayed blood glucose curve in the sugar tolerance test⁵. Y. K. proved no exception. It is very striking, however, that the tolerance curve returned to normal after treatment. (See schema in article quoted.)

Conclusions from the Cretin Experiments—The important fact brought out by this work is the effect of thyroid medication on cretin metabolism. The identical amounts of thyroid which caused nitrogen loss with or without toxicity in normal individuals led to a large gain in nitrogen accompanied with improvement in the clinical condition in the case of the cretin. This effect was so delicate that the nitrogen balance could be used as a gage of the correctness of the dosage. The therapeutic action of the thyroid is therefore anabolic and constructive, not catabolic and destructive. This point will be developed later in the discussion.

With regard to the practical application as to dosage, our observations were necessarily limited to a single patient. It is clearly shown, however, that 0.25 mg. hormone iodine daily is optimal. Kendall has used with success doses varying from 0.125 to 0.333 mg. of hormone iodine in cretinism and myxedema, which our findings corroborate. It is important for the profession to recognize that the optimal tablet dosage is not large, as 0.25 mg. hormone iodine corresponds to about 4 grains thyroid tablets, on the basis that 50 per cent of the iodine content is combined in the active substance. Four grains daily of the standard 0.2 per cent iodine thyroid tablets may be regarded as a preferable trial dose. Hence the practice of prescribing large amounts of thyroid tablets, such as 5 grains three times a day to cretin and myxedema patients, can be expected to be followed by poor results. As, according to Kendall, the active α -iodine varies considerably in various glands, it is easy to understand how uncertain results may follow the use of tablets containing a standard amount of iodine. Thus, it is clear that the isolated hormone, when commercially obtainable, will supersede in reliability all present preparations.

VI EXOPHTHALMIC GOITER EXPERIMENTS

In order to complete our observations, the effect of the thyroid hormone on exophthalmic goiter was studied. The same experimental plan was pursued as hitherto. In connection with varying dietetic régimes, the effect of the thyroid hormone on the nitrogen balance

⁵ Janney, N. W., and Isaacson, V. I. The Blood Sugar in Thyroid and Other Endocrine Diseases, in this issue.

and clinical symptoms was observed. The action of various other thyroid preparations has been frequently studied in exophthalmic goiter, accordingly in our work only the effect of the hormone was investigated.

CASE 5—M F, man, aged 27, Hebrew, hospital orderly. Diagnosis, mild exophthalmic goiter. The family was neurotic but not goitrous. For the previous few months the patient had noticed a swelling of the neck and increasing nervousness. There was found the typical exophthalmic goiter psyche, slight exophthalmos and Stelwagen's sign, slight tremor of hands, increased perspiration, and a diffuse, soft hypertrophy of the thyroid, pulse 80 to 90, palpitation occasionally, no weight or strength had been lost.

This case was selected for study on account of the recent onset and consequent possible greater sensitiveness to hormone treatment. A greatly increased diet, supplying 55 calories per kilogram was given during the entire period of observation. On this diet, combined with

TABLE 5—M F EXOPHTHALMIC GOITER

Period	Date	Change in Weight, lb oz	N Intake, Gm	N in Urine, Gm	N in Feces, Gm	N Balance, Gm	Medication	Diet			
								Prot, Gm	Fat, Gm	Carb., Gm	Cal
1	8/12-18	+ 10	16 17	11 37	1 83	+2 97	- 0	104	153	353	3,817
2	8/19-25	- 4	16 49	10 87	2 85	+2 77	0 01 mg H I				
3	8/26-9/1	- 4	16 30	11 71	1 76	+2 81	0 01 mg H I				
4	9/2-8	+1 0	16 82	11 50	1 70	+3 61	0 005 mg H I				
5	9/10-16	+ 2	16 52	11 25	1 97	+3 30	0 02 mg H I				
6	9/17-23	+ 2	16 47	11 57	1 73	+3 17	0				
7	9/24-30	+ 2	16 46	12 27	1 94	2 25	0				

rest and quiet, M F became rapidly less nervous and excitable before the hormone was administered. An increased nitrogen balance was obtained in Periods 3, 4 and 5 with hormone administration. There seemed in this case to be no definite relation between the amount of nitrogen retained and the thyroid dosage. The clinical condition continued to improve during the entire course of the metabolic study. The pulse decreased in rate to normal, the thyroid swelling grew somewhat less, and the mental state improved. We were, however, unable to trace any definite relationship between a given dosage of the hormone and the clinical improvement. The doses of hormone in this case were minimal, no toxic symptoms having been observed at any time.

CASE 6—J H, man, aged 31, Finn, a carpenter by trade. Diagnosis, exophthalmic goiter. Two brothers and one sister have or had goiter. The sister's eyes were protuberant. One brother recovered after the goiter had been removed. For the previous three years J H had been incapacitated by weak-

ness and nervousness. On account of his poor condition palliative ligation of the superior thyroid arteries was performed by Dr. J. Prescott Grant of the New York Polyclinic Hospital to whose courtesy I am indebted for this case. Operation was followed by improvement for some time. His weight in 1915 was 172 pounds on admission Aug. 31, 1916 it was 118 pounds.

Examination.—Extremely nervous expression, patient thin and weak, musculature poor, twitching of facial muscles, choreiform movements and marked fine tremor of hands, nails thin and seamed, atrophic skin patches, tremor of tongue, teeth defectively calcified, large pulsating thyroid of great density, right lobe large, bruit present, circumference of neck 40 cm., left cardiac border 10 cm. from midsternum, no murmurs, pulse 110 to 120, quick and easily compressible, urine negative.

TABLE 6—J. H. EXOPHTHALMIC GOITER

Period	Date	Change in Weight, lb. oz.	N Intake Gm.	N in Urine, Gm.	N in Feces, Gm.	N Balance, Gm.	Medication	Diet			
								Prot, Gm.	Fat, Gm.	Carb., Gm.	Cal.
1	9/1-6*	— 10	14.93	9.15	2.53	-3.55	0	91	22	404 (9/1-22)	3,029
2	9/16-22†	— 6	14.92	9.19	2.22	-3.51	0.01 mg. H. I.				
3	9/23-29	-2	8.53	8.53	1.71	-1.23	0	5-	6)	272 (9/23-10/6)	1,876
4	9/30-10/6*	— 6	8.56	8.92	1.46	-1.82	0.01 mg. H. I.				
5	10/6-13	-1	11.73	10.23	2.00	-1.43	0	72	167	635 (10/7-11/10)	2,566
6	10/16-22	— 4	11.73	10.28	1.49	-0.03	0.02 mg. H. I.				
7	10/23-29	-1 10	11.73	8.54	1.73	-1.13	0.02 mg. H. I.				
8	10/30-11/5	— 4	11.73	8.33	1.68	-1.74	0.03 mg. H. I.				
9‡	11/6-10‡	-1 8	11.81	8.72	2.26	-0.82	0.03 mg. H. I.				
10	11/16-22	-1 4	13.16	9.42	2.26	-0.48	0	94	92	444 (11/21-12/14)	2,871
11	11/23-29§	— 4	13.22	9.95	1.90	-0.37	0.02 mg. H. I.				
12	12/7-13		15.25	8.62	1.94	-1.61	0.02 mg. M. I.				

* September 10-16 balance omitted, diet unchanged.

† On the following days 9/23-25, 10/6-9, 9/10-12, the balance was omitted to allow the change of diet to have its effect.

‡ Five day balance, patient became toxic.

§ November 20 to December 6 balance omitted, diet unchanged.

This severe case proved a very enlightening study. His state of increased metabolism was well demonstrated in the first two periods (see protocols) where he showed a tendency to lose weight on a diet supplying 3,069 calories or 57 calories per kilogram. The first four periods are chiefly interesting dietetically, the nitrogen balance remaining practically unchanged by the minimal amount of hormone administered. In Periods 6, 7, and 8 an increased dose of hormone (0.02 and 0.03 mg. H. I. daily) caused a decided increase in the nitrogen balance until the patient developed slight toxic symptoms, tachycardia and nervousness in Period 9, with a resulting decline in the balance. The nitrogen balance was again increased in Period 12 with a dose of 0.02 mg. H. I. daily.

This patient's clinical condition became markedly improved during his stay in the ward, but here again it was not possible to trace any definite relation between the thyroid medication or its absence to this improvement

The clinical improvement consisted in a gain in strength, decrease in size of goiter, from 40 cm on Jan 31, 1916, to 37.5 cm on Dec 15, 1916, together with marked change to a softer consistency. The blood Sept 5, 1916, showed hemoglobin, 65 per cent, erythrocytes, 3,900,000, white blood cells, 13,000, neutrophils, 60, small lymphocytes, 34 per cent, large lymphocytes and mononuclears, 6 per cent. After treatment, hemoglobin, 87 per cent, erythrocytes, 5,200,000, white blood cells, 9,400, eosinophils, 2 per cent, neutrophils, 56 per cent, small lymphocytes, 13 per cent, large lymphocytes and large mononuclear cells, 20 per cent, transitionals, 1 per cent.

TABLE 7—J W EXOPHTHALMIC GOITER

Period	Date	Change in Weight, lb oz	N Intake, Gm	N in Urine, Gm	N in Feces, Gm	N Balance, Gm	Medication	Diet			
								Prot, Gm	Fat, Gm	Carb, Gm	Cal
1	11/10-14	— 12	21.42	17.82	1.63	+1.91	None	135	208	204	3,400
2	11/15-19	— 6	21.15	16.10	1.45	+3.59	None			(1/29 4/5)	
3	11/20-27	— 1	21.34	15.79	1.54	+4.00	0.02 mg H I				
4	11/28-3/6	— 8	21.39	15.20	1.59	+4.60	0.06 mg H I				
5	3/1-13	— 4	21.31	14.89	1.63	+4.70	0.06 mg H I				
6	3/14-20	+ 4	21.40	14.80	2.03	+5.29	0.01 mg H I				
7	3/21-27*	— 2	21.38	14.48	1.83	+5.07	0.11 mg H I †				
8	3/31-4/5†	± 0	21.38	14.76	1.90	+4.72	{ 0.22 mg H I † 0.44 mg H I †				
9	4/10-16	+ 12	13.66	11.97	2.00	— 0.31	None	80	86	227	2,070
10	4/17-23	± 0	13.69	11.13	2.00	+0.56	None			(4/6-30)	
11	4/24-30†	— 6	13.66	11.38	1.61	+0.67	None				
12	5/6-11	+ 4	14.50	10.11	1.63	+2.76	None	86	188	280	3,247
13	5/12-18	+ 8	14.48	9.64	1.53	+3.31	None			(4/31-5/6)	
14	5/19-24	+ 4	14.44	9.89	1.46	+3.09	None				

* March 28-30, balance omitted, diet unchanged

† Armour's tablets given, H I calculated

‡ On the following days, 4/6-10, 4/31-5/5, the balance was omitted to allow the change of diet to have its effect

CASE 7—J W, man, aged 35 years, Hebrew, painter by trade. Diagnosis, exophthalmic goiter, mitral insufficiency, quiescent pulmonary tuberculosis. The patient had a history of institutional treatment for tuberculosis in 1912, exophthalmic goiter symptoms since 1916, also swelling of ankles and dyspnea. Examination on admittance Jan 25, 1917, disclosed exhaustion, emaciation, irritating cough, tremor of hands and tongue, abnormal perspiration, dermatographia, cutaneous atrophy, nervous expression of face, marked exophthalmos, the special ocular signs, moderate-sized goiter, tachycardia (100 to 120), slight cardiac enlargement to left, systolic mitral murmur, signs of old apical tuberculosis of right lung, no râles, splenic enlargement, liver 3 cm below costal margin, slight dorsolumbar scoliosis. The urine occasionally showed sugar, discovered in 1916. Blood pressure and blood were normal, nonprotein nitrogen 39.6 mg, and uric acid 2.6 mg per 100 c.c. blood.

There was a distinct increase in the nitrogen balance with thyroid medication until the patient was made toxic in Period 8 with a consequent decline in the retention. The latter part of the experiment (Periods 9 to 14) was devoted to observations on the effect of different diets on the patient's condition (see special section).

The clinical condition of this patient became much improved as a result his stay in the ward. The weakness and ocular symptoms grew less, nervousness and the pulse-rate decreased and the cough subsided. The goiter, however, remained quite unchanged.

Conclusions from the Exophthalmic Goiter Experiments — The impression gained from this work is not encouraging from a therapeutic standpoint, although the cases improved generally while under observation. In one severe case (J. H.) the patient grew strikingly better. These results, however, may just as likely have been due to the effects of rest, better diet and hygienic environment as to the minute amounts of the thyroid hormone administered. The symptoms of toxicity exhibited on such doses do not indicate any possibility that the hormone acts in any way differently from other thyroid preparations in these toxic cases. It is, however, remarkable that in spite of the known tendency to nitrogen loss in exophthalmic goiter, the nitrogen balance became increased when 0.02 mg. H. I. was administered. A possible explanation of this result is reserved for the general discussion.

VII. DIET IN THYROID DISEASE

Diet in Hypothyroidism — In this condition the following facts have been clearly established by previous investigation. The basal metabolism is markedly decreased. Equilibrium is maintained on a diet supplying fewer calories than normal requirement. Few attempts at dietary studies have been made. We therefore subjected our cretin to various dietetic régimes in an effort to determine which ration is most suitable for this condition.

The effect of a high caloric mixed diet was first tried (Protocol Period 1). Although this diet supplied 50 calories per kilogram, the patient lost weight. Her clinical symptoms during this time remained unchanged. A high protein diet of approximately the same caloric value (Period 13) supplying 46 calories per kilogram, caused a considerable retention of nitrogen, but the patient's general condition was not as satisfactory as on the mixed diet. A negative nitrogen balance resulted in Period 10 on a diet supplying nearly as many calories (42 cal. per kg.) and containing a very low protein content, but with approximately the same amount of carbohydrate and fat as was in the high protein diet. Finally a mixed diet of much lower caloric value (31.4 cal. per kg. in Period 21), although not sufficient in itself to

prevent loss of weight, was found to prove very satisfactory for the cretin's needs when taken in conjunction with a therapeutic dose of hormone

According to Falta, in myxedema "the protein requirements are light, and there may be an addition of protein to the body" Our results for cretinism do not bear out this statement that nitrogen is more easily retained. Indeed, the reverse is probably true, otherwise additional nitrogen would not be retained when optimal doses of thyroid are administered, as took place in our experiments

What practical deductions can be drawn from these data? It is evident that (1) in cretinism just as in the case of normal individuals a high protein or a high carbohydrate diet is less advantageous than a mixed diet containing rationally balanced amounts of carbohydrate, protein and fat, (2) diets supplying increased calories do not avail to improve the clinical condition, the reason being that in this disease only a reduced amount of food can be assimilated by the untreated cretin, the remainder of the food being excreted. The amount of food ingested should be gradually increased as the thyroid treatment yields results. Cretins should therefore be maintained on a liberal mixed diet, without attempts at forced feeding

Diet in Hyperthyroidism—The majority of older observers favor the use of a low protein diet in this disease. The few metabolic experiments made with patients do not, however, substantiate this view. This point is clearly brought out by the experiments of Pribram and Porges,⁶ who found the respiratory quotient of this disease unchanged by a low protein, high carbohydrate diet and very properly deduced that the essential condition of these patients remained, therefore, unimproved. On the other hand, a high protein diet with restriction of the carbohydrates, but supplying the same number of calories, produced an increase in the basal metabolism and a loss of weight. The best results were obtained with a mixed diet. Du Bois⁷ in a recent series of exact experiments found that rather less than a normal amount of carbohydrate is consumed in metabolism in these cases. On the other hand, data bearing on this point were reported in the immediately preceding article⁸ in which it was shown that the carbohydrate exerts its sparing effect in preventing nitrogen loss in experimental hyperthyroidism. This result is important as it indicates that a certain, but not necessarily predominant amount of carbohydrate in the diet of hyperthyroid cases is useful in combating the nitrogen loss

6 Pribram, E, and Porges, O. *Wien klin Wchnschr*, 1908, **46**, 1584

7 Du Bois, E. F. *THE ARCHIVES INT MED*, 1916, **17**, 915

8 Janney, N. W., and Isaacson, V. I. *The Effect of Thyroidectomy and Thyroid Diseases on the Protein Metabolites*, in this issue

Our present experiments represent an extension of these investigations. A study of the protocols of the exophthalmic goiter cases shows that the high caloric diet is essential to prevent further loss of weight when weight was being lost. The nitrogen loss in the feces was large, greater than can be accounted for by the increased diet given. This, together with the excessive amounts of the fats frequently found in the dejecta, points to defective intestinal absorption in this condition.

The most favorable diet was found to be one in which the protein, fat and carbohydrate are present in the usual proportions, but in increased amounts. This is well exemplified by the following dietary study.

CASE 8—E T, man, aged 34, Swiss, collector by trade, was referred by courtesy of Dr John Rogers and Dr Eugene F DuBois of the Cornell Medical School. Since 1915 he had been incapacitated with weakness, loss of weight, dyspnea, and diarrhea. On December 31 he was operated on by Dr Rogers

TABLE 8—E T EXOPHTHALMIC GOITER

Diet	Diet					Change in Weight, Lb Oz	N Balance, Gm	Remarks
	Prot, Gm	Fat, Gm	Carb, Gm	Calories	Calories per Kg			
12/ 9-12	95	106	336	2,700	49.6	-1.6	+0.80	
12/13-17	95	137	570	3,218	59.6	± 0	+1.91	Diet unchanged 12/13-1/9
1/14-20	101	211	378	3,912	73.7	+ 6	+3.90	Diet unchanged 1/9-11/3

by ligation of the superior thyroid arteries and removal of tips of both lobes. Improvement followed. He was admitted to the metabolism ward of the Montefiore Hospital, Dec 1, 1916. The patient exhibited some emaciation, a tendency to flushing and perspiration, slight tremor, exophthalmos, von Graefe's sign, dermatographism and a thyroid of normal size but indurated to touch. The left border of the heart was 11.5 cm from midsternum, there was a systolic mitral murmur, temperature normal, respiration 20 to 24, pulse 100, blood count and differential normal.

The dietary studies of this moderately severe case of exophthalmic goiter are abstracted in the table. The patient was under observation in the metabolism ward under the precise conditions described in the preceding pages, with careful estimation of the nitrogen balance. It is seen that weight was lost on a diet quite sufficient to cause a gain in a healthy person (Period 1). A mere increase in the carbohydrate and fat and consequently in the number of calories was sufficient to prevent loss of weight and also to bring about a distinct gain in the nitrogen balance (Period 2). On a still higher caloric mixed diet (Period 3) the weight began to rise and nitrogen was retained in greatly increased amounts.

These results correspond well to previous studies made by Dr Du Bois on the same patient in January, 1915. He found the weight to remain stationary but the nitrogen balance to be markedly positive on a mixed diet of 2,452 to 2,605 calories, which was from 59 to 62 calories per kilogram.

Evidently the dietetic treatment of exophthalmic goiter presents no mysteries. Neither a high protein nor a high carbohydrate diet is followed by as good results as is a mixed diet of adequate caloric value. The same general rules of nutrition hold good in exophthalmic goiter as in the case of normal persons.

VIII GENERAL DISCUSSION

The studies here reported belong to a series of researches aiming at a better understanding of thyroid function in health and disease. Growing out of this work and an extensive critical literary review made necessary by it, several changes in point of view have been reached, which will now be developed.

The general belief in the past with regard to thyroid function, has been that this gland acts normally as a stimulant to metabolism, especially to the protein metabolism. To use the words of von Noorden, the thyroid "stimulates metabolism like a bellows fans a fire." This view has been based on the following points: (1) Ingestion of thyroid material leads to increased metabolism and loss of nitrogen. (2) Myxedema and cretinism are characterized by a general decrease in metabolism, especially by a low gaseous exchange and nitrogen output, which is ascribed to "a lack of the stimulatory effect of the thyroid on metabolism." (3) Exophthalmic goiter is similar to the effects of a large overdose of thyroid substance and is therefore accepted as clinical phenomena due to "hyperthyroidism." A careful scrutiny of the known data has, however, made it very doubtful whether the thyroid problem can best be accounted for in so simple a manner. Our points of view will now be developed in detail.

1 *Anabolic and Catabolic Actions of the Thyroid*⁹—There must be considered the influence of the thyroid on metabolism both in health and disease. It is a well established fact that the usual effect of thyroid taken by normal individuals is loss of nitrogen from the body, sometimes loss of weight, and an increased general metabolism. There exists excellent evidence, however, that under certain circumstances the thyroid can exert practically the opposite effect.

Recent experiments by Schafer¹⁰ and Hewitt¹¹ have afforded valu-

⁹ These views were originally advanced by the writer in December, 1916, at the Annual Meeting of the American Society of Biological Chemists.

¹⁰ Schafer, E. A. *Quart Jour Exper Physiol*, 1912, **5**, 203.

¹¹ Hewitt, J. A. *Quart Jour Exper Physiol*, 1914, **8**, 297.

able data These authors fed thyroid gland to white mice in varying amounts and studied the nitrogen metabolism and body weight The following condensed tabulation has been compiled and calculated from Hewitt's second article These experiments were evidently carefully carried out and the fecal nitrogen was also controlled

From the tabulation it is evident that the *amount* of thyroid gland administered determines its effect on metabolism The feeding of 0.25 gm daily in the second week caused a slight loss in body weight, with a decided decrease in the nitrogen retained In other experiments the feeding of 0.5 and 1.0 gm under the same conditions led to still greater loss of weight and nitrogen When, however, 0.125 gm daily was administered, more food and nitrogen were ingested than under normal dietary conditions or when a larger amount of gland was fed

HEWITT'S THYROID FEEDING EXPERIMENTS

Week	Diet	Food per Kg, Gm	Nitrogen Intake per Kg, Gm	Nitrogen in Urine, per Cent	Nitrogen Retained per Kg, Gm	Gain or Loss in Weight, per Cent
1	Normal period	261	2.66	1.55	1.367	7.0
2	0.25 gm oxy thyroid daily	253	2.53	2.06	1.14	1.7
3	0.125 gm oxy thyroid daily	305	3.26	2.09	1.61	10.4
4	0.25 gm oxy thyroid daily	294	3.20	2.11	1.25	3.3

The urinary nitrogen remained stationary It is, however, very significant that 18 per cent more nitrogen was retained than in the normal period and that the body weight increased 10.4 per cent corresponding to about 50 per cent over and above the total increase noted in the normal period for the same length of time

Experiments with similar results have been recorded by Fonio¹² for myxedema patients Minimal amounts of thyroid compounds caused a gain in nitrogen retention while greater amounts caused loss These experiments are subject to criticism on technical grounds

To understand the significance of these findings one must bear in mind that the thyroid is scarcely second to the hypophysis in exerting a stimulating influence on growth Abolition of thyroid function in the very young leads to stunted growth (cretinism) Proper thyroid medication causes growth to be resumed Cessation of thyroid medication is followed by cessation of growth Experiments carried out on tadpoles illustrate the stimulating effect of the thyroid on growth, as metamorphosis into frogs is greatly accelerated by thyroid feeding¹³

12 Fonio, A Mitt a d grenzgeb d Med u Chir, 1912, 24, 123

13 Gudernatsch, J F Arch Entwickl, 1912, 35, 457, Citronei, G Arch ital biol, 1914, 61, 305

The part played by the nitrogen metabolism in relation to growth is quite well known. A pronounced gain of nitrogen on a proper diet is usually to be regarded as a sign of increased regeneration of tissue or actual growth, for which the nitrogen "gain" of childhood is a good example. *Hence it is evident that a therapeutic action of the thyroid should be found to be accompanied by a gain, not a loss, of nitrogen*

In the present article we have seen how small doses of thyroid suffice to cause clinical improvement in a cretin, which changes were accompanied by an *increased retention of nitrogen*. These experiments were so carefully carried out that we believe them acceptable proof that an increase in the nitrogen balance is an indication of the therapeutic, or anabolic, effect of the thyroid.

But how, then, account for the increased protein metabolism, that is, the increased output of nitrogen following thyroid medication, which is usually accredited to thyroid action? Further investigation and reflection have led us to the conviction that in such cases we are dealing with a toxic rather than a therapeutic effect of the thyroid material and that the loss of nitrogen is very probably a toxic loss.¹⁴

Our present control experiments have shown that the loss of nitrogen may be caused by the slightest overdose of thyroid without necessarily being accompanied by clinical toxic symptoms. Hence it is easy to understand how in the past the thyroid became regarded as normally stimulatory to metabolism.

The thyroid is probably capable of exerting an effect on each cell of the organism (Plummer) by influencing specifically certain metabolites. Among them are to be ranked the carbohydrates and purins, as previous studies⁸ of this series have shown. Experiments by Kendall point to the amino-acids as being directly affected by the thyroid hormone. The carbon-dioxid output is also increased. All these observations emphasize that fundamental changes in the intermediary and basal metabolism are caused by the thyroid whether acting constructively or destructively on tissue, as Bensley's¹⁵ experiments on opossums illustrate. It is entirely possible that this function is accomplished by a selective action on certain articles of the diet through intermediary changes which are at present obscure.

The clear recognition that nitrogen loss following thyroid medication is a toxic manifestation is of practical importance in the thyroid treatment of obesity. It is well known that a rapid loss of weight is to be attained by the use of thyroid tablets in such cases. The malaise

14 The view that the loss of nitrogen following thyroid medication in myxedematous subjects is due to the dissolution of the myxedematous tissue remains an hypothesis without the foundation of experimental proof.

15 Bensley, R. R. *Am Jour Anat*, 1916, **19**, 37.

and weakness which are sometimes exhibited are, however, doubtlessly clinical symptoms of a toxic effect caused by the thyroid as they are accompanied by loss of protein tissue as well as the desired loss of fat. In view of our studies, the use of thyroid in uncomplicated cases of obesity cannot be recommended. I reserve its use, in small doses, to the not uncommon cases of obesity due to thyroid hypofunction.

2 Metabolism in Hypothyroidism—Cretin metabolism is usually characterized in the literature as being "tragic" or inactive ever since the time Magnus-Levy made the remarkable discovery that the basal metabolism is greatly depressed in this condition. Protein metabolism is also regarded as much "reduced", that is, much less nitrogen and nitrogenous substances in general are excreted. These effects are ascribed to the "absence of the stimulatory effect of the thyroid on metabolism." Statements are also made in the textbooks that in cretinism nitrogen is readily retained, that is, protein built up in the body.

Let us now critically study these conceptions. There can be no doubt of the reduction of general metabolism in cretinism as the careful experiments by Du Bois,⁷ using the modern calorimeter, have amply demonstrated. In cretinism little food is taken, with consequent decreased elimination of nitrogen. The reason for this is probably as follows. Only reduced amounts of food can be properly assimilated by the organism, therefore the reduction of intake. That this is true is evident when a cretin is put on a greatly increased diet having abundant protein, as in our case. The increased food fails to be used in tissue repair and upbuilding, with resultant growth such as takes place normally under these circumstances. In consequence *more* nitrogen is actually lost than in the case of a normal person on the same diet. An increased amount of nitrogen is retained with improvement of the clinical symptoms on the same diet when thyroid is administered in proper dosage. Coincidentally the basal metabolism rises to normal owing very probably to the increased assimilative and anabolic processes which may likewise necessitate an increased oxygen intake and carbon dioxide output. *It may then be concluded that the depressed nitrogen excretion in cretinism is not due to "absence of stimulatory effect," but rather to the failure of normal repair and growth processes which are controlled by the thyroid. As these constructive processes are inhibited, little food is taken, for more cannot be assimilated. A low nitrogen output results.* The decreased nitrogen excretion and lowered gaseous metabolism are probably to be accounted for as the result of a compensatory and sparing effort on the part of the human economy, for there are various other examples of like nature known, that is, the mineral metabolism, in which the organism shows a marked ability to conserve necessary materials when they cannot be properly replaced from without.

For the statement that "cretins show a tendency to retain nitrogen easily," we find no experimental proof in an exhaustive study of the pertinent literature. Our experiments clearly show quite the opposite. Indeed, common sense would make it seem impossible that a cretin who suffers from inability to grow, should more easily retain nitrogen, that is, presumably build protein more readily than a normal child. The basis for this false idea is probably that such hypothyroid conditions have been in the past simply regarded as the direct antithesis of hyperthyroidism, in which increased breakdown of protein is well known to occur.

Magnus-Levy and others¹⁶ have accounted for the decreased metabolism of hypothyroidism on the basis of a decreased alimental absorption due to sluggishness of the intestinal tract. Here again, substantiating experimental evidence has been lacking. In a previous research⁵ we have therefore investigated this possibility by means of the nitrogenous excretion. We found no delay in intestinal absorption to follow thyroidectomy in animals. Pari¹⁷ has made similar observations. Additional data covering this point is afforded by our cretin experiments. A study of these protocols makes it clear that the absorption of food, as shown by the nitrogen of the feces, was quite good throughout, demonstrating that the intestinal functions were not disturbed.

The chief difficulty with food assimilation in cretinism evidently lies in the inability of the body to make adequate use of the nitrogenous and probably other food material *after* absorption. The effect of the thyroid medication on the urinary nitrogen (see protocols) gives a clear insight into this. When the dose was therapeutic, definitely less nitrogen was excreted in the urine than without treatment on the same diet. The fecal nitrogen, meanwhile, was not obviously affected. Evidently in their passage through the blood and tissues of the body, more nitrogenous metabolites are retained for constructive purposes as an effect of thyroid treatment.

Cretins and myxedematous individuals are characterized by abnormal adiposity, the deposits sometimes occurring in unusual locations of the body. In seeking an explanation for this metabolic change, attention may be called to our recent studies⁵ on thyroidectomized animals in which a decreased assimilability for sugar was demonstrated. One of the first evidences of a disturbance in carbohydrate metabolism is a tendency to adiposity. Fifty per cent of diabetics are or have been adipose. It seems, therefore, logical to presume that the fat deposits of the hypothyroid conditions are related in origin to the disturbance in carbohydrate metabolism. This view is substantiated

16 Magnus-Levy, A. Von Noorden's Handbuch d. Path. des Stoffwechsels, Berlin, 1907, p. 335.

17 Pari, G. A. Biochem. Ztschr., 1908, **13**, 274.

by extended metabolic studies carried out by us on muscular dystrophy,¹⁸ in which disease abnormal fat depositions are not uncommon, and a similar disturbance in carbohydrate metabolism was found to occur. The reduction of fat in hypothyroid cases undergoing thyroid treatment is not necessarily due to a direct effect of the ingested thyroid on the combustion of the fat, but very possibly is a result of the general

TABLE 9—SPECIMEN DAILY PROTOCOL (S. M., CONTROL)
Diet Protein, 77 gm., Fat, 87 gm., Carbohydrate, 245 gm., Calories, 2,111

Period	Date	N Intake, Gm	N in Urine, Gm	N in Feces, Gm	N Balance, Gm	Medication
3	1916					
	7/23	12.14	8.91			
	7/24	12.14	8.64			
	7/25	12.14	8.94			
	7/26	12.19	9.64	6.67	+13.56	None
	7/27	12.19	9.63			
	7/28	12.14	9.59			
	7/29	11.35	8.71			
4	7/30	10.71	7.98			
	7/31	12.14	8.71			
	8/1	12.14	9.20			
	8/2	12.14	9.17	5.93	+17.67	None
	8/3	12.14	8.65			
	8/4	12.14	8.63			
	8/5	12.14	7.61			
5	8/6	12.14	8.20			
	8/7	12.14	8.86			
	8/8	12.14	8.41			
	8/9	11.44	9.50	6.41	+16.96	0.38 gm. gland
	8/10	12.14	9.54			
	8/11	12.16	7.93			
	8/12	12.15	9.50			
6	8/13	12.14	8.75			
	8/14	12.14	9.21			
	8/15	12.20	8.69			
	8/16	12.20	9.69	7.72	+10.41	0.38 gm. gland
	8/17	12.00	9.29			
	8/18	10.48	9.42			
	8/19	12.08	10.26			
7	8/20	12.18	9.71			
	8/21	12.16	8.02			
	8/22	12.16	9.62			
	8/23	12.17	8.86	10.89	+9.89	5 mg. H. I.
	8/24	12.14	9.25			
	8/25	12.15	8.96			
	8/26	12.14	9.00			
8	8/27	12.20	8.04			
	8/28	12.19	9.74			
	8/29	12.14	8.83			
	8/30	12.19	7.93	5.97	+17.65	None
	8/31	12.20	9.08			
	9/1	12.20	8.33			
	9/2	12.20	8.83			

readjustment of metabolic processes, which are secondary to the anabolic and constructive effects of the administered glandular preparations.

3 *Pathogenesis of Exophthalmic Goiter—Criticism of the Hyperthyroid Theory*—Ever since Kocher published his classic tables con-

18 Janney, N. W., Goodhart, S. P., and Isaacson, V. I. THE ARCHIVES INT. MED., 1918, 21, 188.

trasting the symptoms of hypothyroidism with hyperthyroidism, the conception of "hyperfunction" has been held by most observers to account for exophthalmic goiter. A survey of the evidence, however, some of recent date, renders the acceptance of this view very difficult. These criticisms will now be alluded to in detail.

On a *priori* grounds. When, as in cardiac hypertrophy, increase in the functional activity of an organ occurs, there is always an evident need for the increased activity. The only apparent exception to this rule seems to be acromegaly, but in this condition degenerative processes accompany or soon follow on the overgrowth.

Although the hyperfunctional theory would seem to find a basis in the hyperplasia and hypertrophy found in the great majority of the glands from Graves' disease patients, the exhaustive studies by Wilson¹⁹ and Plummer²⁰ of the rich material of the Mayo Clinic, have emphasized the presence of a considerable "toxic nonhyperplastic" group of cases, presenting a variable histopathology, sometimes degenerative in type. Again, until more is known of the metabolism of thyroid secretion the doubt must remain whether the patches of hypertrophy and hyperplasia found in toxic goiters does not represent a compensatory effort at regeneration of a functionally incapacitated gland. It must also be remembered that certain hyperplastic adenomas of the thyroid are notably nontoxic.

Even the typical exophthalmic goiter contains but $\frac{1}{50}$ to $\frac{1}{20}$ of the total active *a*-iodin present in normal thyroids, according to Kendall and Wilson.²¹ If the hyperthyroid hypothesis were correct, more, not less, iodine should be present in such hyperfunctioning thyroids. Explanations of this discrepancy have been made, but none are supported by good evidence.

Haseman and Walter found that normal thyroid tissue implanted into thyroidectomized rabbits was followed by normal degeneration and regeneration of crushed nerve fibers, which processes took place much more slowly, if at all, when Basedow tumor tissue was thus engrafted. I have, however, been unable to find an accurate description of these striking experiments, which would indicate a lowered functional condition of the exophthalmic goiter and aptly illustrate the part played by the thyroid in the regeneration of tissue.

Exophthalmic goiter is not infrequently found in families having hypothyroid members. The combination of toxic exophthalmic goiter symptoms with hypothyroidism has been frequently observed in the same person. According to Bertine²² of the Cornell Medical School

19 Wilson, L. B. *Am Jour Med Sc*, 1913, **146**, 781.

20 Plummer, H. S. *Am Jour Med Sc*, 1913, **146**, 790.

21 Wilson, L. B., and Kendall, E. C. *Am Jour Med Sc*, 1916, **151**, 79.

22 Bertine, E. *Med Rec*, New York, Nov 18, 1916.

Clinic, they are present in 23 per cent of thyroid cases. This close association of hypothyroid and hyperthyroid symptoms is strongly indicative that the same general cause is present in both conditions. As cretinism and myxedema are unquestionably due to thyroid deficiency, it is likewise probable, in view of the reasons just mentioned, that the thyroid does not function adequately in exophthalmic goiter. Ochsner²³ in an admirable surgical article on hyperthyroidism, concludes that this condition in adolescents is due to growth of the breasts and skeleton at this time, and is comparable to the hyperthyroidism of pregnancy. The large number of "hyperthyroidism" cases developing among army recruits during the training period may likewise be mentioned.²⁴ Such conditions are therefore to be regarded rather as dysfunctional in nature, caused by an overstrain on the gland.

Cases of exophthalmic goiter without tumor are not so very uncommon, which fact is contrary to the hyperthyroid theory. In other cases the tumor recedes but the toxic symptoms continue. Although thyroid medication usually makes exophthalmic goiter patients worse, cases²⁵ have been persistently reported in which the patients have derived benefit from this treatment. This is one of the strongest arguments against the hyperthyroid theory.

Factors which act in lowering the general resistance of the body or of the thyroid are active in the production of exophthalmic goiter. Such are acute thyroiditis, acute infectious fevers and shock. It seems unreasonable that these depressant conditions could produce increased functional activity of any organ including the thyroid.

Similar metabolic disturbances are present in both hyperthyroid and hypothyroid conditions. Thus, the blood sugar tolerance test shows a delayed curve in both instances.⁵ Hypoglycemia, a symptom of hypothyroidism, is sometimes present in exophthalmic goiter.²⁶ Creatin is present in the urine of both hyperthyroidism and hypothyroidism.

The blood picture of exophthalmic goiter (characterized by reduction of the neutrophils, lymphocytosis and mononucleosis²⁷) is practically identical with that of myxedema and cretinism.²⁸ If these con-

23 Ochsner, A. J. *Ann Surg*, 1916, **64**, 385.

24 Verbal communication of Major Harlow Brooks, M. R. C., Camp Upton.

25 Murray, G. R. *Twentieth Century Practice of Medicine*, New York, 1895, **4**, 804; Buschau, G. *Basedow'sche Krankheit*, Leipzig, 1894; Strumpell, A. *Textbook of Medicine*, New York, 1911, p. 581.

26 Writer's observation.

27 Caro, L. *Berl klin Wchnschr*, 1908, **45**, 1755; Kocher, Th. *Arch f klin Chir*, 1908, **87**, 131; Klose, H., Lampe, A. E., and Lisevang, R. E. *Beitr z klin Chir*, 1912, **77**, 601.

28 Klose, H. *Ergebn inn Med u Kinderh*, 1913, **10**, 167; Fomo, A. *Mitt a d Grenzgeb d Med u Chir*, 1912, **24**, 123.

ditions are diametrically opposed, such a striking similarity in the metabolic and hematologic picture would scarcely be found

The foregoing considerations seem sufficient to show the inadequacy of the hyperthyroid theory of exophthalmic goiter to account for the known facts

THE HORMONE HYPOTHESIS OF THYROID TOXEMIA AND EXOPHTHALMIC GOITER

If we then discard the hyperthyroid theory, we have but one remaining explanation, "dysfunction" of the thyroid as the cause of exophthalmic goiter. The difficulty has been to formulate any view of the pathogenesis of exophthalmic goiter on a dysfunctional basis which is not open to serious criticism. The hypothesis which will now be developed has slowly matured. It seems to explain most of the facts fairly adequately in view of present knowledge. It is, however, fully recognized by me that it, too, lacks proof. It has value merely as a working hypothesis until future researches either prove or disprove its usefulness.

The most convincing argument in favor of the hyperthyroid theory has been the fact that the ingestion of large amounts of thyroid preparations leads to toxic symptoms, even including exophthalmos, which may become identical with the disease exophthalmic goiter²⁹. Several other well authenticated cases are known.

The facts, then, are these. Many or all the toxic symptoms of Graves' disease may appear in connection with (1) pathologic changes in the thyroid gland, that is, exophthalmic goiter, (2) as a result of administration of thyroid material or *thyroid hormone* in excess to normal, myxedematous or thyroidless human beings, or animals. A logical consideration of this situation leads to the deduction that the thyroid hormone itself is capable, in overdose, of producing the toxic phenomena accompanying exophthalmic goiter, as it produces this effect both in the presence of nonfunctioning thyroids or in the entire absence of this gland from the body. The experiments of Kendall and myself, in which we observed the symptoms of hyperthyroidism from the injection of overdoses of thyroid hormone, afford still more definite evidence in this regard. We have, therefore, to seek the toxic causative agent in the thyroid hormone.

The toxic manifestations require a latent period of from twenty-four to forty-eight hours for their development (Kendall, Janney), which time may be required for the changes to take place in the hormone itself before symptoms are produced. It is likely that the hormone, when present in the body in excess, is subject to the general laws

29 Notthafft, v, A F Zentralbl f inn Med, 1898, 19, 353

of catabolism, just as is any related cyclic chemical substance provided with a side chain. Such an example is the normally occurring amino-acid, tryptophane, likewise containing the indol group, which yields in the intestine the putrefactive products indol and skatol. Chemically

TABLE 10—SPECIMEN DAILY PROTOCOL (Y K, CRETIN)

Period	Date 1916	N Intake, Gm	N in Urine, Gm	N in Feces, Gm	N Balance, Gm	Medication	Remarks		
1	3/13	10.54	8.47	3.25	+9.70	None	(For diets see Table 4)		
	3/14	10.54	7.90						
	3/15	10.55	8.41						
	3/16	10.53	9.88						
	3/17	10.54	7.75						
	3/18	10.54	7.74						
	3/19	10.54	7.18						
2	3/28	10.54	6.84	1.50	+16.99	0.5 gm gland	Diet changed		
	3/29	10.54	6.98	1.02					
	3/30	10.56	6.67	0.53					
	3/31	10.54	7.29	1.70					
	4/ 1	10.52	7.65	0.70					
	4/ 2	10.54	6.62	1.37					
	4/ 3	10.54	7.40	0.47					
3	4/ 4	10.54	7.44	0.93	+18.37	0.5 gm gland		Diet changed	
	4/ 5	10.51	7.21	1.41					
	4/ 6	10.52	7.19	0.31					
	4/ 7	10.56	6.70	0.79					
	4/ 8	10.51	6.70	0.78					
	4/ 9	10.51	6.76	2.15					
	4/10	10.54	6.64	0.40					
10	6/ 4				-0.08	None			Diet changed
	6/14	4.31	4.01	5.80					
	6/15	4.31	4.27						
	6/16	4.31	3.31						
	6/17	4.31	3.18						
	6/18	4.32	3.23						
	6/19	4.31	3.31						
6/20	4.30	3.11							
11	6/21-27						Menstrual period omitted		
	6/28	4.31	2.75	0.27	+4.70	0.5 gm gland			
	6/29	4.31	3.08	1.15					
	6/30	4.31	3.04	0.65					
	7/ 1	4.31	2.61	0.82					
	7/ 2	4.31	2.77	0.90					
	7/ 3	4.31	3.12	0.49					
7/ 4	4.31	3.05	0.77						
21	10/ 6	8.04	6.76	3.21	+0.64	None	Menstrual period omitted		
	10/ 7	8.00	7.88						
	10/ 8	7.67	7.26						
	10/ 9	8.00	7.12						
	10/10	8.00	6.84						
	10/13-17								
22	10/18	8.00	6.25	4.81	+9.27	0.25 mg H I		Menstrual period omitted	
	10/19	8.04	5.91						
	10/20	8.09	6.17						
	10/21	8.00	5.66						
	10/22	8.00	6.22						
	10/23	8.04	6.05						
	10/24	8.00	5.83						
23	11/25	8.04	5.49	5.30	+7.02	None			Menstrual period omitted
	11/26	8.00	6.00						
	11/27	8.09	6.05						
	11/28	8.00	6.50						
	11/29	8.04	6.94						
	11/30	8.11	6.84						
	11/31	8.00	6.14						

considered, it is entirely possible that the thyroid hormone which, according to Kendall, contains the indol nucleus, should be split into intermediary decomposition products, one or more of which may be toxic and produce the symptoms designated as hyperthyroidism

The symptoms of exophthalmic goiter may be divided into two groups (1) toxic symptoms, (2) symptoms of thyroid deficiency. Group 1 contains most of the frequently occurring and striking phenomena, consequently the significance of the second group has usually remained disregarded. Group 1 includes psychic stimulation, tremor, tachycardia, lability of the sympathetic nervous system, loss of weight and nitrogen, increased basal metabolism and tendency to rise of temperature. Group 2 includes goiter, cutaneous symptoms (atrophy, pigmentation, scleroma, brittleness and loss of hair, trophic nail changes), abnormal depositions of subcutaneous fat (rare), osseous changes (imperfect ossification and epiphyseal union) fatty degeneration, especially of the heart³⁰ and somatic musculature, mononucleosis, metabolic disturbances similar to or identical with those in hypothyroidism—delayed glucose assimilation, creatinuria, growth disturbances in youthful cases. Certain symptoms such as weakness, loss of weight and creatinuria may properly be ascribed to either group.

With regard to the pathogenesis of this complex symptomatology, the following may be said. The toxic symptoms of exophthalmic goiter have been traced in the foregoing to the thyroid hormone itself, and are probably due to the development of toxic products produced in its metabolism. All evidence tends to indicate that the thyroid hormone is a synthetic product. It is certainly built up by the thyroid from inorganic iodine and other substances possibly related to the indol-containing amino-acid, tryptophane. It is possible that one or more of these intermediate substances is toxic, and, indeed, identical with the products arising in the breakdown of the hormone in the body. It is likewise possible that various factors might disturb the normal synthesis of the hormone, the result being the premature discharge of the toxic intermediary product into the circulation. The factors producing this condition might be disturbances in the nervous control of the thyroid metabolism, such as could be produced by fright, emotion, shock or direct organic injury such as trauma, thyroiditis, or again, histologic and gross changes in the parenchyma of the gland, that is, the well known causes of exophthalmic goiter.

The result of the premature discharge of the hypothetical toxic intermediary product would be an impoverishment of the gland of the thyroid hormone, which would explain the fact that Graves' disease goiters are poor in iodine, and especially in the active *alpha*-iodine pro-

30 Wilson, L. B. Collected Papers of the Mayo Clinic, 1915, 7, 438

tems The decreased production of the normal hormone due to the cause mentioned would tend to be accompanied or followed by the signs of thyroid insufficiency Thus the deficiency symptoms (Group 2) can be accounted for, also the concomitant occurrence of hypothyroid and hyperthyroid symptoms, and the tendency of exophthalmic goiter patients to develop myxedema

The frequent failure of the pathologic picture to coincide with the clinical (see the foregoing) can best be explained by these views, which do not strictly necessitate histologic change at the beginning, but rather a defective endocrine secretory metabolism as to the ultimate cause of exophthalmic goiter

According to our hypothesis there is present in the thyroid and blood of exophthalmic goiter patients a toxic substance This view is substantiated by the experiments of Caro,³¹ confirmed by Klose by demonstrating the toxicity of the urine from exophthalmic goiter patients, also recently by Blackford and Sanford,³² who found a depressor substance in the thyroid and serums of such patients

Lampe, Liesgang and Klose in their voluminous monograph on Graves' Disease have developed a hypothesis somewhat similar to the foregoing The failure of these authors to put forth an adequate explanation for the symptoms of hyperthyroidism resulting from the ingestion of normal thyroid material has, however, prevented acceptance of their views

There remains to interpret the thyroid treatment of exophthalmic goiter with the aid of the hypothesis just advanced The results obtained by us were (1) clinical improvement in some cases, unchanged condition in others, (2) increase in the nitrogen balance in all cases studied The uncertainty of the effects on the clinical condition may have been due to the fact that our cases, all of which were selected before the development of the theoretical views here presented, were of the toxic type It must be borne in mind that the introduction of normal hormone from without may not necessarily lead to a cessation of the chemopathologic processes causing the toxic symptoms of this disease This may, indeed, prove an effectual barrier against obtaining results by thyroid, or, indeed, any medical treatment in such cases Again, the dosage employed may not have been suitable, or the treatment sufficiently protracted It seems insignificant, however, that the nitrogen balance improved in all cases and at times seemed to bear a relation to the amount of the thyroid hormone administered As this same effect was also observed in hypothyroidism, but never occurred in the normal controls, it certainly suggests that thyroid defi-

31 Caro, L Quoted in Klose, H, *Erbe d inn Med u Kinderh*, 1913, 10, 167

32 Blackford, J M, and Sanford, A H *Am Jour Med Sc*, 1913, 146, 790

ciency is an underlying condition in exophthalmic goiter. Our results indicate, however, that in accordance with previous experience the thyroid treatment of these toxic cases is inadvisable.

In exophthalmic goiter showing deficiency symptoms, judicious thyroid treatment would, according to our views, be indicated. Such a case has been studied with great thoroughness by Halverson, Bergeim and Hawk³³. On 6 to 9 grains of thyroid extract daily, improvement of the clinical symptoms occurred, accompanied by a marked retention of nitrogen, calcium, magnesium, sulphur and phosphorus. Thymus had the opposite effect. It is possible that further study will demonstrate generally the value of thyroid therapy in cases of thyroid toxemia with deficiency phenomena provided they are properly selected and continuously treated.

I desire to acknowledge the excellent assistance rendered by Miss Maude Hays in the dietetic and analytical work of this research.

³³ Halverson, J. O., Bergeim, O., and Hawk, P. B. *THE ARCHIVES INT MED*, 1916, **18**, 800.

THE NITRITOID CRISES AFTER ARSPHENAMIN INJECTIONS ~

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HISTORICAL

Soon after the introduction of arsphenamin, in 1910, reports began to appear in the literature of untoward effects, severe reactions, and even deaths following its use intravenously. The most important papers on the subject, now grown quite voluminous, will be given in the bibliography¹. All the different types of reactions, from simple transient fever to fatal acute hemorrhagic encephalitis or nephritis were considered. No attempt was made at first to separate out of the complexa any distinct groups or types of symptoms. As a result, much confusion and misunderstanding in the description, tabulation, interpretation and explanation of these was produced.

Gradually, one type of clinical picture occurring during or immediately after an intravenous arsphenamin injection, began to stand out. The chief symptoms were redness of the face, dyspnea, a feeling of anguish and distress, cough and precordial pain. It was described first probably by Notthaft in 1911. In his case, collapse followed an injection of insufficiently alkalinized arsphenamin. Nevertheless he did not believe it due to the relative acidity of the solution, as he had observed a similar reaction with a prepared properly alkaline solution. In the same year, Levens published several cases of anaphylactoid symptoms after a second arsphenamin injection. Wechselmann was the first to theorize about the problem. According to him, it was caused by water contaminated by dead bacteria, molds or dissolved protein used in dissolving the arsphenamin. With freshly distilled water, he claimed, all untoward effects could be prevented. Marschalko in 1911 reported an anaphylactoid reaction after a first injection of 0.28 gm arsphenamin, and regarded it due to molds in the water. Fischer in the same year reported a case of acute hemorrhagic encephalitis after a second injection of arsphenamin. Hoffmann and Jaffe simultaneously described anaphylactoid symptoms follow-

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* Salvarsan is the trade brand of the preparation of arsphenamin referred to in this article

1 The references will be found in alphabetical sequence at the end of the article

ing second arsphenamin treatments. They attempted transmission to animals, by sensitizing them with patient's serum, but they could not succeed.

In 1912 more comprehensive studies of these phenomena appeared. Iwaschenzow reported a series of 15 cases with anaphylactoid symptoms immediately after or during arsphenamin injection. He rightly emphasized their distinction from the later symptoms of acute or subacute arsenical poisoning with which Wechsellmann had concerned himself or those which Ehrlich thought were caused by arsenoxid and which resemble so closely the symptoms of carbon monoxid poisoning. He concluded that the symptoms appearing immediately after or during the injection were definitely not caused by protein or organic substances in the water used, but depended on a sensitized condition of the patient which in turn varied with the dose and the interval elapsing between injections. Bruckler in the same year described nine cases. Of these, two occurred at the third injection, one at the seventh, two at the eighth, two at the ninth, and two at the tenth, in all stages, ages and varieties of syphilis.

A Frenchman, Millian, now began to publish on the subject papers presented to the *Societe francaise de dermatologie et de syphilis*. To the complex of symptoms under discussion he gave the name of nitritoid crises, because of their similarity to those of amyl nitrite poisoning. Also, as the latter were amenable to epinephrin treatment, he applied it to the former, and obtained good prophylactic and therapeutic results.

In the same year, A. F. Swift published a paper on anaphylaxis to arsphenamin. He analyzed a series of cases, in three cases the reaction appeared at the fourth injection, in two at the fifth, in three at the sixth, and in one at the seventh. Skin hypersensitiveness was present in some of his patients. A condition of anti-anaphylaxis was apparently produced in one of his cases ten minutes after. He worked on the mechanism of the reaction. It will be considered later.

A number of other publications, to be mentioned in the bibliography, elaborating these fundamental clinical facts, but none contributing anything new to the symptomatology, or natural history, of the reaction, have appeared.

THEORIES TO EXPLAIN THE NITRITOID CRISES

With the reports of these symptoms, speculation about their meaning of course began. Wechsellmann's views about the importance of contaminated water really applied only to the delayed symptoms after arsphenamin. Iwaschenzow, as said, completely exploded their value for the control of the nitritoid crisis. Attention was now paid to two

other factors one, that of the sensitization of the patient to arsphenamin, in the anaphylactic sense, second, the acidity and concentration of the solution, and its physicochemical effect on the blood. Hoffmann and Joffe attempted to sensitize guinea-pigs to the serum of their patients, afterwards injecting arsphenamin, but obtained negative results. Auer tried to sensitize guinea-pigs directly with arsphenamin, but failed. Swift, however, using a mixture of serum and arsphenamin, was able to shock animals, getting the picture of acute anaphylaxis. Brauer, in 1912, also failed in direct sensitization of animals with the serum of patients.

As early as 1910 Willige, describing the details of a death due to arsphenamin, suggested that the concentration of the drug might be the cause of the fatality. At the same time, Hering emphasized the acidity as a factor. He varied the amount of acidity in experiments on animals. Frankel and Groven reported a death due to 0.4 gm arsphenamin in 15 c c water, to which only 1.5 c c of normal sodium hydroxid solution was added. In 1911, Michaelis, speaking of the use of arsphenamin intravenously in acid solution, mentioned the therapeutic possibility that the drug was precipitated in the circulation by the alkalinity of the blood. That year Schottmüller claimed that acid arsphenamin added to serum *in vitro* produced a precipitate. Miessner reported extensive studies on animals. He found that the severity of the reaction, both in normal animals, and in those with foot-and-mouth disease, varied directly with the acidity. If the arsphenamin was alkaline, 400 mg per kilogram could be given with impunity. On the other hand, 5 mg per kilogram of a 0.5 per cent acid solution caused dyspnea and often death. Necropsy showed all the organs normal except the lungs, which showed a thrombosis of the blood vessels and an inflammatory exudate in the parenchyma. He also obtained a precipitate *in vitro* with acid arsphenamin and serum, and thought the thrombosis due to precipitates in the pulmonary capillaries. Fleig got the same results at about the same time but claimed the essential factor was not the hydroxyl but the phenol radical in the arsphenamin.

Three Americans now made important contributions to the problem. Auer, who had failed to produce arsphenamin anaphylaxis in animals, now demonstrated that the toxicity was inversely proportional to the acidity and concentration. This is a law that must be considered in any explanation of the nitritoid crisis. Then Don Joseph showed first that alkaline solutions, no matter if strong or weak, in large dose or small, given rapidly or slowly, produced no bad effects. Acid solutions, if highly diluted (0.6 gm in 300 c c), acted likewise. If stronger, the latter caused death. A heavy pre-

precipitate was found nearly always in the right ventricle and in the lungs. Finally, MacKee proved that the weight of the precipitate in vitro varied directly as the acidity and concentration.

Two other theories should be mentioned. That of Millian is that a vasodilatation is responsible for the symptoms. This obviously begs the questions at issue. Schamberg has lately put forward the theory that the symptoms are due to the by products formed in the manufacture of arsphenamin, which he calls the substance *x*. This, like the theory of Swift, does not relate itself to the fundamental laws of the effect of acidity and concentration, or of precipitate formation, and so leaves unexplained most of the phenomena. Nor does it explain why, out of a group of persons treated with the same batch of arsphenamin, only one or two will react.

THE PROBLEM STILL TO BE SOLVED

A problem still remained. Although, as a result of the work on the importance of acidity and concentration, the use of thoroughly alkalinized arsphenamin became general, and there was a great reduction in the number of reactions, a few patients still continued to react to the most carefully alkalinized solutions injected with a technic *lege artis*. In them, it occurred generally after one injection had previously been given, and, having once happened, could be predicted to recur. The problem of the mechanism of these reactions the writer set himself to solve.

In a series of 300 consecutive arsphenamin injections eleven individuals were found who suffered from nitritoid crises when treated with properly prepared, alkalinized arsphenamin. Four of these had them on three successive occasions, and one on four. In the last case, the reaction was predicted. Saline solution, prepared as the arsphenamin solution was prepared failed to elicit the symptoms. Arsphenamin almost immediately (after the entry of 30 cc), produced the symptoms of the nitritoid crisis. Serum was obtained from these and from the nonreacting patients. When properly alkalinized arsphenamin was brought into contact with these serums, those from the nonreacting produced no, or a little, opalescent precipitate. Those from the eleven reacting, however, caused a heavy whitish yellow precipitate. Thus, by testing previously the serum and the solution one could say whether or not a reaction would follow the injection. In those in whom a precipitate was produced, a prophylactic dose of epinephrin seemed to prevent the onset of the nitritoid crisis. After its appearance, also, the same drug hypodermically shortened the duration of the alarming symptoms.

Having determined that the nitritoid crisis occurring with sufficiently alkaline arsphenamin in certain persons was due to intravascular precipitation (whereas previously it had been accepted that only acid salvarsan could do this), the next question that arose was, Why should the precipitate be formed only in the blood of these patients and not in that of the majority who received the same amount of drug in the same physical state? Fleig had shown that most of the precipitate produced when acid arsphenamin was added to serum consisted of protein. No determinations of the content of the blood in protein in these cases had ever been made. Blood from two patients analyzed by the nephelometric method of Kober and Graves showed that there was an increased protein content essentially an increased globulin content. The hypothesis may therefore be put forward tentatively of course, in view of the small number of studied cases that this may be the solution of the problem that is that the increased protein content of the blood in certain syphilitics may favor precipitation *in vivo* even of properly alkalinized arsphenamin. To confirm this, of course, the blood protein of a number of syphilitics should be studied.

SUMMARY

All the data on the nitritoid crises may be explained as follows. Either because of the acidity of the injected arsphenamin or because of the increased protein especially globulin content of the blood of certain syphilitics, intravascular precipitate formation occurs. This precipitate is responsible for the local vasodilatations, which constitute the essence of the crises. Such symptoms may be expected to follow other modes of causing intravascular precipitations. The writer has seen the symptoms of the nitritoid crisis appear after a gelatin injection given intravenously. The theories of neither Swift nor Schamberg throw light on the fundamental laws of the toxicity of arsphenamin established and confirmed by so many researches. The one fact alone that all the symptoms of the nitritoid crisis may be produced in a normal individual by a single injection of arsphenamin in an acid solution is enough to dispose of the sensitization theory of Swift. And as Iwaschenzow pointed out years ago the fact that the same lot of arsphenamin given to a whole series of patients will produce the reaction in perhaps one or two puts out of court any special toxic substance theory, like that recently revived by Schamberg. The other theories, without either factual or experimental support are too numerous to mention.

To sum up. In a series of 300 arsphenamin injections eleven patients reacted with the symptoms of the nitritoid crisis. The serum of these patients contained substances which precipitated with the

arsphenamin in vitro, and probably also in vivo, causing the symptoms by a consequent vasodilatation, controllable by epinephrin subcutaneously. The serum of two of these patients contained an increased amount of protein, especially globulin.

I wish to express my indebtedness to Dr H. Goldenberg, attending dermatologist at the Mt. Sinai Hospital, New York, for permission to study these cases.

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A CLINICAL REPORT OF NONSPECIFIC PROTEIN THERAPY IN THE TREATMENT OF ARTHRITIS

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Twenty-five years ago Rumpf expressed the opinion that the beneficial effects observed following the subcutaneous injections of a vaccine were the results of a nonspecific immunologic reaction. It has been only during the past five years that his contention has received serious attention from the medical profession.

In 1893, Fraenkel¹ demonstrated that he could favorably influence the clinical course of his typhoid fever patients by treating them with subcutaneous injections of killed typhoid bacilli. His associate, Rumpf,² went a step further and employed killed pyocyanous bacilli instead of the typhoid bacilli. Since he obtained equally good results, he felt that he was justified in claiming that the beneficial reaction was of nonspecific character. However, Ehrlich's theory of the specificity of all immunologic reactions had such firm footing among the members of the medical profession that they refused to consider seriously the idea of a nonspecific therapy. In 1913, Victor Vaughan³ revived interest in this question by publishing his book on the relation of protein split products to immunity and disease.

During the past three years a number of workers have contributed to our knowledge on this subject. As a result of the work of Kraus,⁴ Ichikawa,⁵ Ludke,⁶ Saxl,⁷ Novy,⁸ Jobling,⁹ Peterson,¹⁰ Coley,¹¹ Miller

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1 Fraenkel Ueber Spezifische Behandlung des Abdominal Typhus, Deutsch med Wchnschr, 1893, **19**, 958

2 Rumpf Die Behandlung des Typhus Abdominalis mit Abgetoteten Kulturen des Bacillus Pyocyanous, Deutsch med Wchnschr, 1893, **19**, 561

3 Vaughan, V C Protein Split Products in Relation to Immunity and Disease, 1913

4 Kraus and Mazza Zur Frage der Vakzine Therapie des Typhus Abdominalis, Munchen med Wchnschr, 1914, **61**, 1967

5 Ichikawa Abortive Treatment of Typhoid and Paratyphoid, Sei-i-Kwai Med Jour, 1913, **33**, 73

6 Ludke Behandlung abdominal Typhus mit Intravenosen Injektionen von Albumosen, Munchen med Wchnschr, 1916, **63**, 571

7 Saxl, P Ueber die Einwirkung Pyrogenes Substanzen und Fieber, Munchen med Wchnschr, 1916, **63**, 571

8 Novy and de Kruif Jour Am Med Assn, 1916, **66**, 2031

and Lusk,¹² and Culver,¹³ it has become apparent that in the future this form of treatment will deserve a definite place in our list of therapeutic procedures

Because at present this treatment is still in the experimental stage, and the clinical reports of large series of cases treated by the intravenous administration of a foreign protein are relatively few, the following report is submitted with a view to confirming its undoubted value in a large percentage of the cases. No satisfactory explanation for the beneficial results obtained by the use of this type of therapy has as yet been advanced, although numerous investigators are working on the subject at present.

We are indebted to Miller and Lusk for the suggestion of treating arthritis by intravenous injections of foreign proteins. They have reported that in their treatment of 175 cases of acute, subacute, and chronic arthritis (uncomplicated by adhesions) they obtained favorable results. Cecil¹⁴ confirmed this opinion on a series of forty cases of acute arthritis. In this work, inasmuch as we have not attempted to restrict the type of cases to be treated, but have included practically all cases complaining of joint symptoms which have come to the City Hospital during the past six months, as well as the chronic cases, with or without adhesions, which were in the wards previous to the beginning of the treatment, we feel that we have given this method of treatment a severe test.

I am indebted to Drs. Shelby, Wightman, Qumby, Bastedo, and McCabe for the courtesy of allowing me to use the cases in both medical divisions, and to Dr. Larkin and his assistants for the dilution and administration of the vaccines.

The essential fact to keep in mind in connection with this report is that the reaction was produced as a result of the introduction of a foreign protein, or, to be more exact, a bacterial endotoxin into the blood stream. The following are a few of the different foreign proteins which have been successfully used in the treatment of arthritis: Killed typhoid,¹⁵ gonococci,¹³ colon and meningococcus bacilli and proteose.

9 Jobling THE ARCHIVES INT MED, 1917, 19, 1042

10 Jobling and Peterson Jour Am Med Assn, 1916, 66, 1753

11 Coley Treatment of Malignant Inoperable Tumors, with Toxins of Bacillus Erysipelas and Bacillus Prodigiosus. Read before Third International Conference of Cancer Research, Brussels, 1913

12 Miller and Lusk Jour Am Med Assn, 1916, 66, 1756

13 Culver Verhandl des Deutsch Gesellsch f Urol, 1913, 4, 102 Abstr in Jour Am Med Assn, 1917, 68, 362

14 Cecil THE ARCHIVES INT MED, 1917, 20, 951

15 Miller, J. L. Jour Am Med Assn, 1917, 69, 765

In other words, one may select a bacterial, an animal, or a vegetable protein as a therapeutic agent. The clinical reaction is apparently the same following the intravenous injection of any split protein, although the required doses vary with the different proteins. In our treatment only one type of foreign protein was used, because very little is known as to the dangers of the treatment and its contraindications. It might be mentioned that although we have had not bad results, Thomas¹⁶ declares he knows of several cases in which the treatment was followed by sudden death. With the exception of one case of hypertension, all of these patients cited by Thomas were apparently in such a serious condition at the time the vaccine was administered that they should not have been considered suitable cases for the treatment.

Typhoid vaccine from the laboratories of the board of health was used in our work. Our decision in this matter was influenced by the consideration that it would be easy to make this method of treatment accessible to the general practitioner in the future if the initial success should prove to be of permanent character. This was contrary to the advice of Miller and Lusk, who said that they were unable to obtain reliable results from stock vaccines. They used their own freshly prepared vaccines. But as the New York Board of Health laboratory products are universally accepted as standard, a thorough trial was considered advisable before condemning them. The dose of vaccine was administered in 10 c.c. of freshly prepared physiologic sodium chlorid solution.

As this type of treatment has not been extensively used, it is perhaps wise to describe in detail the effects of the most important clinical phenomena which have been observed in our series of cases.

1 *Chill* — The injection of a foreign protein intravenously is followed after a half hour by a severe chill. It is similar in many respects to the severe chills seen in a malarial paroxysm. The entire body shakes violently. In chronic cases, these involuntary muscular contractions probably play an important part in breaking up numerous small adhesions and thus account for the increased mobility of the joints. The violence of the muscular contractions would contraindicate the use of this type of treatment during pregnancy, on account of the danger of abortion, or in the third week of typhoid on account of the danger of perforation, or hemorrhage. The chill lasts for from twenty to thirty minutes, although occasionally the patient feels chilly for from ten to eighteen hours. During the chill, the patient should have extra blankets and hot water bottles.

16 Thomas, H. B. Jour. Am. Med. Assn., 1917, 69, 770

2 *Temperature*.—A rise in temperature accompanies the chill. In moderate reactions the temperature usually goes up to 103 F. In a more severe reaction the temperature may reach 106 or 107. The patient should not be sponged or given drugs to counteract the high temperature while the general condition is good and while the pulse remains normal. As a rule we have found that the improvement of the patient's symptoms corresponds very closely with the height of the temperature reaction. Our most striking beneficial results have been in cases in which the temperature rose to 105 and 106. Even in these cases we have never seen evidence of cardiac or respiratory distress. It is interesting to note that a number of observers have found that high temperatures artificially produced have a deleterious effect on the life and growth of the organisms of any established infections.¹⁷ Ludke believed that the infecting organism was either killed by the high temperature or that a more rapid and more firm union of the antigen and antibody resulted. However, since many of our joint cases are due to gonorrheal infections the susceptibility of this particular germ to heat should be appreciated as any marked increase in temperature destroys the life of this organism. It has been shown experimentally¹⁸ that it is impossible to infect a patient with gonorrhea while suffering from an acute infectious disease if the temperature at the time is 102 or over. Culver¹³ quotes a case of acute urethritis of three days' duration showing typical gonococci in the smears when the patient was admitted to the hospital. On the following day the patient had a chill followed by a temperature of 105. Malarial parasites were found in the blood. The chills and fever were allowed to continue for four days at the end of which time the discharge had stopped and no gonococci could be found in the urethra or in the urine. It must be emphasized, however, that the striking therapeutic results obtained in cases of arthritis could not consistently be attributed to the beneficial effects of fever alone as the streptococcus and other organisms generally associated with this condition are not particularly sensitive to heat.

3 *Profuse Perspiration*.—Following the chill the patient's entire body is covered by a profuse perspiration. It has a very foul odor and is strongly acid to litmus.

4 *Headache*.—This occurs in almost every case. As a rule it is only moderate and of short duration; occasionally it is very severe and may last as long as twenty-four hours. Miller and Lusk warn us against the use of this treatment in alcoholic patients inasmuch as it is inclined to cause a dangerous delirium.

17 Cited by Kyaw. *Med. Klin.*, 1912, 8, 1829.

18 Boerner and Santos. *Med. Klin.*, 1904, 10, 1062.

5 *Backache*—In about 50 per cent of the cases the patients complain of a severe pain in the back. This is usually bilateral, and sometimes radiates down toward the groin. In this respect it may simulate renal colic or acute renal congestion.

6 *Abdominal Pain*—There is frequently pain in the abdomen associated with nausea and vomiting. We have noted that these symptoms almost invariably occur if the vaccines are given on a full stomach, and in cases which have not had a preliminary cathartic. Occasionally, in severe reactions, the patients have mild hematemesis. Five of our cases showed moderate gastric hemorrhages. The hemorrhage in one case persisted for a week. Although at the time the gastric hemorrhages all occurred in association with very severe reaction and high temperature, yet these patients subsequently showed the most marked clinical improvement.

7 *Pain in the Affected Joints*—At the height of the chill, and for a few hours subsequent to it the patients almost always complain of an increase in the pain in the affected joints. This is probably due to the violent contraction and mechanical irritation produced as a result of the chill. If the pain is moderate, it can usually be controlled by small doses of acetylsalicylic acid. If the pain is severe, it is sometimes necessary to use from one eighth to one quarter grain of morphin.

8 *Blood Changes*—1 The red cells. The red cells tested before and following the chill show no difference in their fragility. In some cases we have noted that there is a slight temporary hemolysis present following the chill. The same dose will sometimes produce slight hemolysis in one case and not in another. Hemoglobin estimations do not show any marked variation during the course of the treatment.

2 Leukocytes. Following the administration of the vaccine, there is a mild leukocytosis. Coincident with the chill, the leukocytes rapidly decrease in numbers. Usually they average 3,000 or 4,000. This in turn is followed immediately after the chill by a second leukocytosis. It usually reaches from 20,000 to 30,000, but in severe cases it may rise to 50,000 to 75,000. The increase is almost entirely due to polymorphonuclear leukocytes. At the end of twenty-four hours the leukocyte count has usually returned to normal. Jobling warns us that "We must not overemphasize the therapeutic importance of the leukocytosis, because even normal rabbits respond with a marked leukocytosis to the intravenous injection of typhoid vaccine"¹⁹. He

19 McWilliams, Helen. Jour Immunol, 1916, 1, 259

also reminds us that "Although splendid results have been obtained by this type of treatment in typhoid fever, the normal course of recovery in typhoid is not marked by a leukocytosis"

9 *Kidney Changes*—As a great many of these patients complain of a severe pain in the back, one naturally asks whether it can be possible that this form of treatment has injurious effects on the kidney. This phase of the subject has been particularly interesting since Longcope²⁰ published his article in which he claims to have produced lesions simulating those of acute and chronic nephritis in experimental animals as a result of repeated anaphylactic shocks. His contention is worthy of careful consideration and study, although it is somewhat doubtful as to whether it can be applied in cases of human nephritis. As these reactions are apparently a mild form of anaphylactic shock, it would appear, according to Longcope's theory, that we should have some evidence of renal injury in our cases of arthritis treated by this method. A number of the chronic cases have received from fifteen to forty injections, whereas most of the animals in his series were killed after having received ten injections. None of our patients has shown evidence of acute kidney injury, even after the most severe shock.

By "acute kidney injury" is meant the presence of a trace of albumin, or of macroscopic red blood cells in the urine. In the cases which had a trace of albumin and a few casts in the urine previous to the administration of the vaccine, no appreciable increase in these elements has been detected.

In a report of very careful work on this subject, presented at the meeting of the American Pathological Society in Philadelphia, April 5, 1918, Bell and Larson began by explaining that Longcope claimed to have found 15 per cent more glomerular lesions in his animals which had been subjected to repeated anaphylactic shock than were found in the control series of apparently normal animals. Although he endeavored to exclude unsuspected or spontaneous lesions of the kidney by carefully selecting young and healthy animals for his work, he admitted having used a few animals showing mild albuminuria. In only two or three of these did he take the precaution of examining the kidney previous to the administration of anaphylactic shocks. Bell and Larson made an effort to improve on his method. They first stated that in examining different series of laboratory animals, there is a wide variation in the percentage of the cases showing glomerular lesions at necropsy. In one series of apparently healthy animals

²⁰ Longcope. Production of Experimental Nephritis by Repeated Protein Intoxication, Jour. Exper. Med., 1913, 18, 678.

80 per cent showed glomerular lesions, whereas we ordinarily expect to find only about 30 per cent showing glomerular lesions. It is not always possible to detect the presence of these lesions in the kidney, even by the most careful examination of the urine. It is therefore not safe to assume that an animal has no healed glomerular lesions on the evidence that it appears healthy and has a negative urine. They also took the extra precaution to operate in every case in order to examine the surface of the kidney for evidence of scars or small inflammatory areas previous to the administration of the foreign protein. No animal was accepted which showed either of these lesions or albuminuria. In their conclusions they say that they were unable to determine that the production of mild anaphylactic shocks in animals had a deleterious influence on the kidney. This conclusion would be in direct accord with our clinical results and with those of Culver.

10 *Blood Pressure*—Miller and Lusk said in their paper that in their opinion a high blood pressure was a contraindication to this form of treatment. For this reason, and also as a part of the study of its effect on the kidney, the blood pressures were carefully taken in the last sixty cases included in this report. It was found that the blood pressure during the chill is usually raised fifteen to twenty points. Following the chill, it is usually lowered ten to twenty points below normal, and remains low from one to three days. In only two cases did it show a moderate rise. In one patient with a marked hypertension, the blood pressure dropped forty points. It remained low for two or three days and gradually returned to its former position. The treatment apparently had no ill effect on the condition of the patient.

11 *Heart*—In this series, the treatment was used in ten cases of heart disease, two of mitral stenosis, three of aortic regurgitation, and five of mitral regurgitation. All of these patients were well compensated, and apparently were unaffected by the administration of the vaccine. One patient with mitral stenosis was admitted suffering from acute multiple arthritis of a very severe type. Salicylates and acetylsalicylic acid were tried for one week without affecting the temperature or improving the patient's general condition. He was given twenty million killed typhoid bacilli intravenously during the late afternoon. The following morning he was much improved. His temperature and joint symptoms, which showed a tendency to recur at irregular intervals for a period of two weeks, were easily controlled by repeating the vaccine. The patient secured a position as orderly and remained under observation for over four months without any recurrence of his symptoms. Apparently, the heart lesion remained unchanged. The other case of mitral stenosis was promptly and permanently relieved.

from precordial pain by the administration of one dose of vaccine Luthlein²¹ reported a case of gonorrheal endocarditis successfully treated in this manner.

Up to the present time no bad cardiac symptoms or signs have been observed as a result of the patients being allowed to get out of bed and walk about the wards. We have found that it is apparently unnecessary to keep the patients in bed except during the day when they receive the vaccine.

RESULTS

In reporting on the efficacy of this therapeutic procedure it is difficult to give an absolutely accurate report without going into the minute details of each case. Our report includes 110 patients treated during the past eleven months. For the sake of brevity we have grouped the cases and have attempted to give an impartial report of our clinical results.

Acute Cases—In about 60 per cent of the cases one injection abruptly terminated the acute attack. A large majority of them had been unsuccessfully treated by the usual rheumatic remedies before coming to the hospital. Thirty per cent required from one to five injections. The greater number of these obtained immediate relief from pain although the permanency of the cure has not been established. Ten per cent were unimproved.

Subacute Cases—In this class we included the cases of less than one year's duration not showing ankylosis. After repeated injections marked improvement was obtained in 50 per cent. of these cases, considerable improvement in 25 per cent. and only slight improvement in the remaining 25 per cent.

From our observation up to date it would seem that the greatest improvement follows the first dose. It was frequently noted that intractable or obstinate cases did not improve until we had given doses sufficiently large to produce a severe reaction. Sometimes one severe reaction was sufficient; at other times it required several marked reactions to effect a definite improvement in the patient's condition.

Chronic Cases—This class included cases which have persisted for periods lasting from one to ten years, even those with marked ankylosis. A moderate improvement in the mobility of some of the joints was noted in almost all cases. This increased mobility was particularly noted in the joints of the upper extremities. Even a small improvement is a cause for gratitude in the patient as it allows him increased ability to use his hands and arms.

²¹ Luthlein. *Wien. klin. Wchnschr.* 1915 28, 533, *Jour. Am. Med. Assn.* Feb. 3, 1917.

PRECAUTIONS TO BE OBSERVED

As this method of treatment is still in its infancy, a word of caution is in order. Rufus Cole advises that before the foreign protein therapeutic treatment is given to the general practitioner, experimental medicine should determine its dangers. Miller and Lusk conclude their report with the following warning: "This form of therapy is still in the experimental stage, and should not generally be applied without first a careful consideration of the dangers associated with it."

The most important dangers and contraindications which we have noted in our work up to the present time are

- 1 Hemolysis may occur as a result of the intravenous use of distilled water, therefore, always dilute the stock vaccine with sterile normal salt solution

- 2 Start the treatment by using small doses—five to ten millions. The average dose is considered to be about fifty millions, and the maximum dose about two hundred and fifty millions. We have frequently used much larger doses, but following these larger doses the reaction is uncertain, and sometimes dangerous. In this connection, Jobling says

It is almost impossible to determine beforehand the degree of reaction which will follow these intravenous injections. Some authors believe that it depends on the severity of the disease, while others consider the concentration of immune bodies in the circulating blood more important. From a general survey of the work done, however, it appears that there is some other factor as yet unknown which plays an important part in determining the severity of the reaction.

- 3 If a typhoid vaccine is used as a foreign protein therapeutic agent, it is necessary to remember that if only one dose has been given, the patient is sensitized to typhoid infection. To minimize danger, at least two more injections should be given—subcutaneously if necessary—in order to desensitize the patient. The second and third injections should be given within six days' interval after the first injection.

- 4 Before using any vaccine, inquire carefully as to the previous history of anaphylactic phenomena. Then follow up the treatment with the same type of vaccine throughout. We have had only two cases which gave mild anaphylactic symptoms. No cases of severe anaphylaxis have been reported so far in the literature, when a typhoid vaccine was used.

CONCLUSIONS

- 1 It has been found that intravenous injections of foreign proteins are apparently more efficacious than the usual drug treatment for the relief of cases suffering from acute, subacute, and chronic

arthritis In making this statement, due consideration has been given to the known variation in duration of an attack of acute rheumatic fever

2 In some cases there is a tendency to recurrence, with symptoms milder in type A large proportion of these patients can be greatly benefited by intensive treatment The percentage of these recurrences is no larger, if as large, as we are accustomed to see in the patients treated by drug therapy

3 There is no evidence up to date that the foreign protein injections have an injurious effect on the kidneys

4 Treatment is not dangerous if the foregoing precautions are observed

5 Vaccines prepared at the Laboratory of the Board of Health give reliable and uniform results

SEROLOGIC LOCALIZATION OF ORGANIC BRAIN LESIONS *

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CHICAGO

During my work on dementia precox, the dialysis method of Abderhalden, slightly modified, proved to be of great value. Yet, as this method did not, for certain reasons, become very popular, I thought it imperative to show that if used properly it is quite reliable and more than that, it can be of great value in the clinical diagnosis of obscure cases.

It seemed advisable to attempt to localize by this method those gross brain lesions which could be verified either by an operation or by necropsy, or by unmistakable clinical evidence. The technic used in all experiments was a modification of the original method based on nearly 4,000 tests, was easy to perform, less complicated and perfectly reliable. The detailed description of this modification will be found in the latter part of this article.

In the cases in which the dialysis method has been used for the purpose of a focal brain diagnosis, twenty-five have been sufficiently studied clinically or verified by operation or necropsy to be considered. The clinical diagnosis or symptoms were not known to me in most of the cases of this series. The serum was delivered for examination with only the general information that the patient suffered from some brain lesion, the location of which was not even suggested, but which I was requested to locate by serologic means. After the test was made and the diagnosis from the test was noted, it was given to the clinician for final comparison.

In the general table (Table 1) summarizing the results, the portions of the brain ("substrates") taken for the single tests are named by Roman and Arabic numbers. Figures 1 and 2¹ show the gyri which correspond to the numbers in Table 1 and in the text. Table 2 represents the subcortical structures under III and IV.

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* From the Psychopathic Hospital of Cook County

* Part of the work reported in this paper was conducted in the Otho S. A. Sprague Memorial Institute, another part in the Memorial Institute for Infectious Diseases

¹ Figures 1 and 2 are adapted from pictures in the "Human Anatomy" of Spalteholz

TABLE 1

[illegible]

* I₂₃ Broca's convolution

* I₂₈ Broca's convolution

† II₁₉ Island of Reil[illegible]

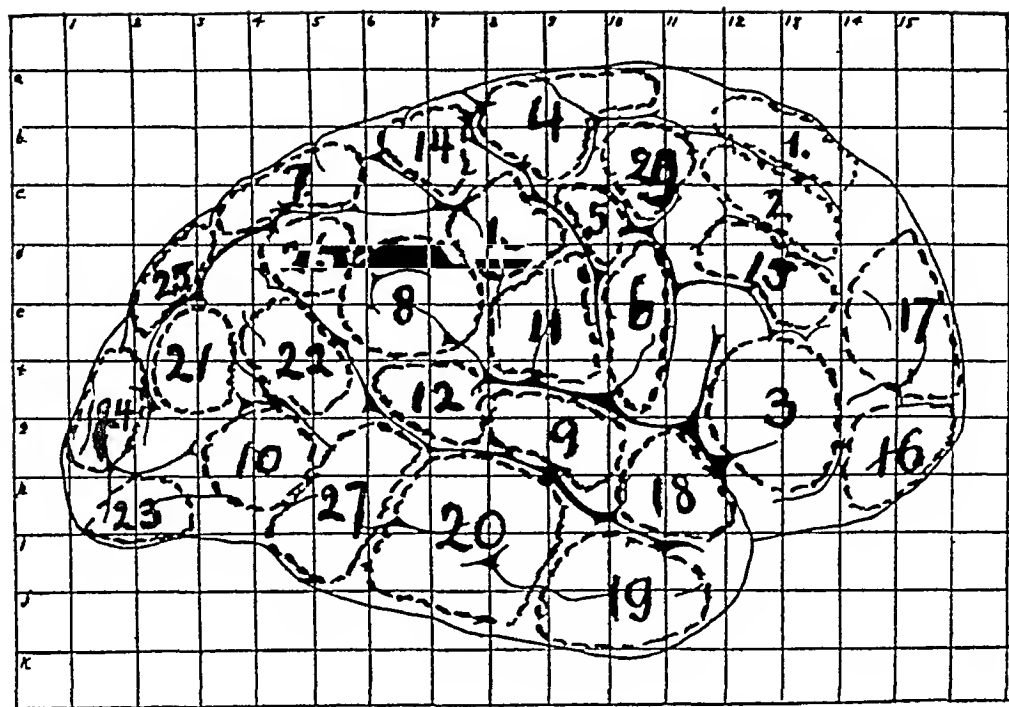


Fig 1—The areas of the brain cortex

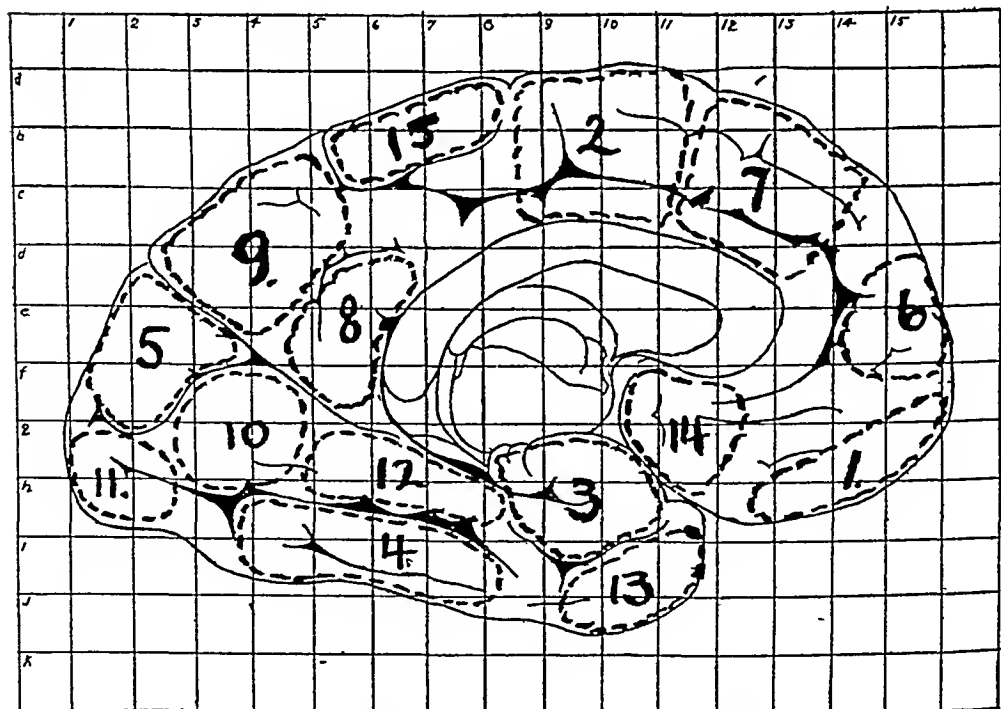


Fig 2—The mesial surface of the brain

TABLE 2—SUBCORTICAL STRUCTURES UNDER III AND IV, TABLE 1

III	1 Spinal cord, upper curvature	13 Pineal gland (human)
	2 Medulla and lemniscus	14 Corpora quadrigemina
	3 Pons	15 Corpus callosum
	4 Corpus mamillare	IV 1 Pineal gland (cattle)
	5 Chiasma opticum	2 Pituitary (cattle, anterior)
	6 Pituitary (whole, human)	3 Pituitary (cattle, posterior)
	7 Olfactory tract and bulb	4 Infundibulum (cattle)
	8 Fornix	5 Dura
	9 Caudate nucleus	6 Cerebellar gray matter
	10 Optic thalamus	7 Dentate nucleus
	11 Geniculate body (lateral)	8 Internal capsule
	12 Choroid plexus	9 Lentiform nucleus

APPARATUS AND TECHNIC

Dialyzers—They are made of collodion in the following way A 10 per cent solution of well dried celloidin shreds in equal parts of alcohol and ether is filled into tubes ¾ by 4 inches (best with far outstanding rims, so-called fat melting point tubes). The tube is now reversed and the collodion is allowed to flow directly back into the bottle for one minute The tube is then reversed again and allowed to stand another minute upright, until a small drop collects on the bottom of the tube The tube is reversed again, the ring of collodion permitted to reach about the half of the height of the tube and turned back into position Through turning of the tube the solution is now distributed evenly on the lower part of the tube After a short experience one is able to judge just how much of the solution to let accumulate on the bottom in order to obtain a good thin tube with enough strength in the bottom to prevent folding in

The ether vapor is blown out from the inside of the tube, which next is filled with 80 per cent alcohol After allowing it to stand for about twenty minutes, the alchol is poured out and the tube, with the collodion film, immersed in cool running water After all the alcohol is washed out, which takes place after about thirty minutes, the rim is loosened, and the dialyzer can now be easily pulled out If the dialyzer made in this way has no air bubbles and is evenly shaped, it can be used without testing It is advisable to reject without test all those which are either uneven or too white (they ought to be just slightly milky), or if they contain in the wall, and especially on the bottom, any air bubbles There is too much danger of breaking the very much thinner wall of air bubbles and making the dialyzer leak and consequently losing the experiment The dialyzers are preserved in 80 per cent alcohol and washed for half an hour in running water before every test They can be used over and over again, only care must be taken to remove all the serum after every use For that end it is advisable to wash them first in physiologic sodium chlorid solution to prevent any globulins from precipitating, and afterward in running water for at least one hour They ought to be in alcohol for at least six hours between tests in order to sterilize them

Dialyzers made in this way keep very well for many months, are ready for use at short notice, and are uniform in action

The way of making them was adapted, with some changes, from a similar method by Pregl²

Dialyzing Flasks—Instead of the expensive Erlenmeyers with wide neck, as recommended by Abderhalden, I am using ordinary wide-mouthed, tall-form 3-ounce bottles The advantage of these bottles is the low price, and what is more important, the possibility of utilizing a much taller column of water for dialysis, thus proportionally to the dialyzing surface increasing the rate of dialysis

2 Pregl Fermentforschung, 1914, 1, 1

Water—Ordinary distilled water (neutral to litmus) is used

Serum—The blood is usually taken from any of the large veins in the arm with just enough constriction not to suppress the pulse entirely. A short needle, gage 16, was found most suitable because, while not making too big a hole in the vessel, it allows the collection of the necessary volume of blood quickly, thus preventing any annoyance to the patient. About 3 or 4 ounces of blood are collected into dry sterile bottles without the use of any anti-coagulant. The blood is allowed to stand for an hour or so at room temperature, then the clot is torn to smaller pieces with sterile long hatpins and separated well from the glass, and the container left in the ice-box for several hours (over night). The serum is poured off into centrifuge tubes and centrifugated at medium speed for about ten minutes. The clear serum is pipetted off into a dry sterile graduated cylinder.

The serum should not show much hemoglobin, although that does not interfere markedly with the reaction, according to my experience. In the same way it is not essential to take blood outside of the digestive period, though it seems to give a clearer cut experiment to do so. Presence of bile in blood does not interfere with the reaction, beyond staining the dialyzers.

Substrates—As material for my brain tissues, human brains from necropsies were used. Only brains from individuals perfectly normal, as far as the brain was concerned, were used and care was taken to use as fresh material as possible (not more than ten hours after death) to avoid postmortem changes in the tissues.

All the large vessels were removed and pieces cut out as marked in Table 2 and Figures 1 and 2. In slicing off pieces from the cortex, care was taken to remove only the gray matter, the parts from inside the fissures not being utilized at all. The pieces were cut into small particles of the size of a small pea and left stand for some time in labeled flasks filled with tap water, preferably in the ice-box. Every two hours the water was changed until all traces of blood disappeared. Now distilled water was used in the same way, and lastly distilled water with 0.5 per cent acetic acid. After all the blood was removed from the tissue in this way, the pieces were coagulated by immersing for about two minutes in boiling water. The tissue was fished out, put back into the labeled flask and extracted cold two or three times with alcohol and as many times with ether in order to remove all fat and lipoids. When a drop of extracting fluid does not leave any fat on evaporation on a watch glass, the tissue is ready for freeing it from dialyzable substances giving the ninhydrin reaction. That is accomplished by immersing the particles in boiling water for not more than five minutes and repeating the procedure several times with fresh water. Care must be taken not to prolong the boiling too much, because then we run the danger of hydrolyzing or boiling off the specific protein. The boiling is repeated until 10 cc of the water in which the tissue was boiled ceases to give a reaction with 0.2 cc of a 1 per cent ninhydrin solution on boiling for about three minutes, that is, until about 2 cc are left in the tube. The tissue is now transferred to sterile bottles, covered with boiling distilled water and about $\frac{1}{2}$ inch of toluene. If the bottles are properly corked and the pieces, when necessary, taken out under aseptic conditions, the tissues thus prepared keep almost indefinitely. Just before the test the substrate is boiled three times, for a short while each, in distilled water.

Test Tubes—The test tubes should not alkalinize the water on boiling and therefore only the best quality should be used—Jena, Nonsol, or best of all, Pyrex. The test tubes and the flasks are always cleaned with chromic acid.

The Test—Into each of the dialyzing bottles 10 cc of neutral distilled water is measured with a pipet. The washed dialyzer is taken into the left (scrubbed) hand, a piece of the chosen substrate inserted into it carefully with a long forceps and from 0.7 to 1 cc of the clear serum added. The charged dialyzer, after being provided with a half inch layer of toluene over the

serum is put into the bottle, a few drops of toluene dropped on the water and all covered with a watch glass. As many dialyzers are charged as different substrates are to be used and every bottle is labeled to avoid confusion. Besides those tissue dialyzers an odd number (three or five) of serum control tubes (without any substrates) are rigged up in the same way. All bottles are left for twenty hours in an incubator regulated at between 26 and 30 C. This low temperature was chosen as it is sufficient for the digestion while it is not high enough to spoil the dialyzers by promoting in any very marked degree the hydrolysis of celloidin which being an ester is hydrolyzible.

After twenty hours' incubation the water from the outside of the dialyzer is transferred into alkali-free test tubes. The contents are boiled for a short time to drive off the toluene, 2 drops of a 1 per cent. solution of ninhydrin are added and the contents of the tube again boiled briskly until only a $\frac{1}{2}$ inch high layer is left in the test tube. If in the case of bumping or foaming the liquid becomes turbid or precipitates the test is rejected because of the possibility of the presence of protein due to a leaky dialyzer. If on the other hand the liquid remains clear but refuses to boil quietly one or more short glass capillaries (sealed on the upper end) may be dropped into the tube.

The reading is made at least half an hour after the last tube is boiled in which time the equilibrium is surely reached. The reading is made by comparison with the control tubes which sometimes are slightly colored. This may be due either to presence in the serum of digestive ferments or amino-acids and peptones if the blood was taken during digestion or was slightly hemolyzed. After a short experience this fact does not make any difficulties. The control tube is considered negative. Three plus was the designation given to the color which appears when 5 cc. of a 0.1 per cent solution of asparagin and 2 drops of the ninhydrin are added to a boiled cow's control tube and the contents boiled as in all other tests. The intermediate colors are called 2 and 1 plus.

After the ninhydrin test is read the reactions are painted with colored inks—white, blue, violet, and red (3 plus)—on charts identical with Figures 1 and 2 as well as a figure indicating the subcortical structures of Table 2 but printed on transparent paper thus showing after overimposing in transmitting light all the reactions in various levels at a time, and allowing the determination of the localization of the lesion.

RESULTS OF TESTS

CASE 1—W. V. Psychopathic Hospital Chicago Jan 3 1916 Brain tumor. Only seven different brain tissues were used as substrates. In this and the two following experiments a mixture of all the parts of the cortex was used as substrate without differentiation. An exceedingly strong reaction with the pituitary tells the localization. Clinically acromegaly.

CASE 2—Mr P. Psychopathic Hospital Chicago Feb 8 1916 Brain tumor. Ten different substrates were used. The reaction with the anterior pituitary (3 plus) indicates the localization of the lesion, as would be expected according to a clinical diagnosis of acromegaly.

CASE 3—Mr N. Cook County Hospital Feb 8 1916 Clinical Diagnosis, brain tumor. Nine different substrates were used. The cerebellar gray matter and the pons gave strong positive reactions. A necropsy performed a week later by Dr. Bissel pathologist of Cook County Hospital revealed a tumor in the cerebellopontine angle.

CASE 4—A. F. Presbyterian Hospital, Chicago Dr. R. Wilder June 8 1916 Clinical diagnosis known to me, pituitary gland disease (sexual precocity). Fourteen substrates were used. The double negative reaction with the pituitary gland excludes that structure. The lesion is localized in the posterior lobe of the hypophysis (III. and IV.) representing probably hypofunction, which would

produce sexual symptoms similar to those due to pineal trouble Clinical diagnosis afterward changed to posterior pituitary insufficiency

CASE 5—L D Cook County Hospital Dr R. Hamill, May 18, 1916 Clinical findings, motor aphasia and right body hemiparesis Eighteen different substrates were used The most pronounced reactions are in the optic thalamus, pons, frontal cortex and the Broca convolution

CASE 5a—Same case. June 22, 1916, shows practically the same reactions, with only slight differences in intensity of positiveness

CASE 6—J F Presbyterian Hospital, Chicago Dr D Lewis, June 23, 1916 Brain tumor Fourteen different substrates used The most important reactions are in the pituitary (III_c—3 plus) and especially its frontal lobe (IV_s—3 plus) and the occipital vision center (II_s—2 plus) Localization The lesion is in the anterior hypophysis, visual trouble Clinically, acromegaly, blindness

CASE 7—G J Psychopathic Hospital, Chicago, April 16, 1917. Twenty-one different tissues used as brain substrates The reaction (3 plus) with the occipital vision center (II_s), and the anterior pituitary (IV_s—3 plus) suggest the localization of the lesion in the hypophysis A subsequent roentgen-ray examination reveals a very small sella turcica, posterior clinoid processes much enlarged and possible pituitary hypoplasia Clinically, visual delusions

CASE 8—Em F May 24, 1917 Twenty-one different substrates were used Besides a 2 plus reaction in the pituitary (anterior), there is a prominent reaction with the visual center in the occipital lobe The patient later gave a history of having suffered several years from double vision, but the relation of this to the reaction, if any, is not clear

CASE 9—Mr T Psychopathic Hospital, Chicago, Aug 8, 1917 Clinical diagnosis, violent mania with visual hallucinations Forty different substrates used The motor area of the cortex shows throughout positive reactions (I_{1,2,3} and II₂), while the positive reactions with visual path represented by the cuneus (II_s—2 plus) the corpora quadrigemina (III₁—2 plus) and the lateral geniculate bodies (III₁₁—3 plus) correspond with the visual delusions

CASE 10—A G Dr A Heym, Nov 9, 1917 Diagnosis, brain tumor Thirty-four different substrates were used The motor area in the cortex shows very pronounced positive reactions (I_{1,2,3}) The pituitary gives strong reactions (2 plus—III_c, IV₂) The lesion lies in the anterior lobe of the pituitary Clinical diagnosis, acromegaly with occasional epileptiform attacks

CASE 11—J M Psychopathic Hospital, Chicago, Nov 26, 1917 Dr G W Hall Clinical diagnosis, tumor in the left frontal lobe Thirty-four different substrates were used The lesion was apparently cortical, because all non-cortical tissues reacted negatively (III and IV) and lies clearly in the frontal lobe (I_{1,2,3} are 3 plus positive) Because of too small a number of different parts of the frontal cortex used for the test, no nearer localization could be attempted The clinical findings, in short, were the following Trauma three months previously, rapid mental deterioration for the previous month, disorientation, emotionalism, recognized objects but could not name them, general tremor, jerking of right arm at times In the beginning of February the patient died after a second trephining (in the left frontal region) and on necropsy, performed by Dr LeCount, was found a glioma of the left parietal lobe in the neighborhood of the base of the temporal lobe

CASE 12—F A. Presbyterian Hospital, Chicago, Dec 6, 1917 Dr Thor Rothstein Diagnosis, brain tumor Fifty-nine different substrates were used All the positive reactions in the frontal, central, parietal and occipital lobes could be centered by the association tracts in the temporal lobe and especially in its basal part Here, too, were the two most pronounced reactions (I_s and II_s) Pathology in that region would very well explain the reaction with the corpora quadrigemina (III₁) and the cerebellar gray matter (IV_s) It seems

that the lesion was located in the base of the temporal lobe in its white matter and that the pressure was directed mostly toward the adjoining parts of the cerebellum and possibly the corpora quadrigemina

The clinical findings related to me after finishing the test were the following Pupils large and equal, right does not respond to light or accommodation, left sluggishly, vision in right practically absent, distinct temporal hemianopsia in the left, no evidence of involvement of cranial nerves, rigid neck, passive motion in all directions causes pain, which is also the cause of difficulty in rising from recumbent position, vomiting, fainting spells, all reflexes normal, spinal pressure 265 Clinical diagnosis, tumor of the hypophysis Since the patient left the hospital without being operated on, neither the clinical nor the serologic diagnosis could be confirmed

CASE 13—S S Cook County Hospital, Jan 28, 1918 Dr G W Hall Diagnosis, probably brain tumor Fifty-nine different substrates were used The lesion was evidently cortical, since all the most pronounced reactions appeared in the convex surface ($I_{2,3,6,13,20}$ —3 plus) All of these areas could be centralized through the association fibers in I_3 Hence the localization of the lesion in the upper part of the third frontal convolution Clinically, tumor in the right frontal lobe

CASE 14—Stan G Cook County Hospital, Jan 28, 1918 Dr Hamill Aphasia and right body hemiplegia Fifty-seven different substrates were used The 3 plus reaction with the Broca convolution suggested aphasia Three plus reactions with the lower anterior central convolution is accounted for, on one hand, by the strong reaction with the internal capsule (2 plus— IV_6), on the other hand, by an apparent degeneration of fibers connecting the motor area with the base of the caput nuclei caudati (3 plus— III_b) and running thence through the corpus subthalamicum and the lemniscus (III_2 —1 plus)

Thus the lesion, of whatever nature it is, must lie in the lower portion of the anterior central gyrus and Broca's convolution, causing aphasia, right body hemiplegia, and probably involvement of the fifth, seventh, and twelfth cranial nerves which originate in said area

CASE 15—V B Cook County Hospital, Feb 11, 1918 Dr Hamill Aphasia Sixty-one different substrates were used The reaction shows diffuse changes following pretty closely the areas supplied by the middle cerebral artery and especially its external striate branch, so that only a hemorrhage or thrombosis can be suggested without any centralized localization Clinical diagnosis, thrombosis involving the Broca convolution

CASE 16—T K Aug 31, 1917 Cook County Hospital The following clinical diagnosis was given to me subsequent to the completion of the test Sudden blindness from secondary optic atrophy, probable cause, serous meningitis

The test was performed with forty different substrates The strongest reaction (3 plus) was with the cuneus and corpora quadrigemina, 2 plus with the optic chiasm In short, the test was strongly positive with the visual fibers of the brain, and indicated that some pathologic process involved these fibers This entirely corresponded with the clinical symptoms as already stated

CASE 17—C D Sept 24, 1917 Cook County Hospital Dr G W Hall Clinical diagnosis, possible brain abscess or cerebral thrombosis

The reactions, which were made with thirty-six different substrates, were, when positive, located almost only in the cortex and apparently scattered The frontal lobe (I_1 — I_2 — I_5 —see Fig 1) proved to be strongly positive, though the corpus callosum, corpus mammillare, and the medulla reacted slightly positively The path of the association indicated that the posterior part of the second frontal convolution was the probable seat of the lesion (point between I_2 — I_4 — I_6)

The necropsy performed by Dr John Nuzum, pathologist of the Cook County Hospital, revealed a solitary abscess in exactly this place

CASE 18—H S Oct 3, 1917 Presbyterian Hospital, Chicago Dr P Bassoe Clinical diagnosis, brain tumor The reaction was tested with forty different substrates and indicated in the first place that the lesion was not in the cortex. The most pronounced reactions were with the cerebellar gray matter (IV₆), with the dentate nucleus (IV₋), anterior pituitary and the corpus callosum The final diagnosis from the test was lesion in the cerebellum, which was found at the operation in the form of a large cyst of the upper frontal part of the cerebellum

CASE 19—M O'B Presbyterian Hospital, Chicago Dr James B Herrick Clinical diagnosis, brain tumor Forty substrates were used The strongest reactions were with the posterior pituitary, with the chiasm the lateral geniculate bodies (III₁₁), the cuneus (II₂), the olfactory bulb (III₋) and the uncus (II₂)

The strong positive reaction with the optic chiasm explains the 2 plus with the vision center in the occipital lobe, especially because the reaction with the lateral geniculate body was 3 plus, thus completing the number of positive reactions throughout the central visual path The 2 plus reaction with the olfactory apparatus, due probably to pressure from the pituitary, suggests an olfactory disturbance, a fact which would explain the 2 plus reaction with the olfactory sensory area (II₂) This suggestion is still more upheld by the 2 plus reaction with the corpus mammillare (III₄), which, as known, holds some relation to the sense of smell The reaction with the thalamus (III₁₀) probably can be explained as involvement secondary to that of the corpus mammillare, possibly through the fasciculus thalamo-mammillare (bundle of Vicq d'Azyr) The 2 plus reaction with the choroid plexus would indicate intracranial pressure Thus the localization of the lesion in the posterior pituitary

After delivery of the complete report the following clinical and laboratory details were given Diagnosis of tumor in the hypophysis, roentgen-ray examination shows great destruction in the sella turcica Ophthalmologic examination Visual field of left side destroyed almost completely, in the right eye very much subnormal Almost complete loss of smell on the left side as compared with the right side.

CASE 20—Mrs H Oct 18, 1917 Presbyterian Hospital, Chicago Dr P Bassoe Clinical diagnosis, brain tumor Forty different substrates were used The most pronounced reactions were in the fornix (III₂), the optic chiasm (III₂) and the anterior pituitary (IV₂), 2 plus reactions in the optic thalamus (III₁₀) and the choroid plexus (III₁₂), a weak reaction with the caudate nucleus (III₂), the other part of the hypophysis (IV₂), the olfactory apparatus (III₋) and the corpus callosum (III₁₂)

Since there was a general diagnosis of tumor, an attempt was made to localize it in one of the enumerated structures A lesion in the pituitary or in the chiasm causing such strong reaction would undoubtedly cause visual disturbances and reflect on the geniculate bodies, corpora quadrigemina and the visual center in the sensory area of the occipital lobe, since these parts gave negative reactions the localization was to be in the fornix or the thalamus, and it was decided that it was most likely in the fornix, because a lesion in the thalamus probably would have brought about secondarily some cortical reactions which are missing

After delivery of my report and localization I was informed that clinically there was no localized lesion, but an internal hydrocephalus of the third ventricle with pressure directed mostly toward its frontal wall The reactions obtained in the test, as can be seen, are in no way contradictory to that diagnosis Only the posterior wall of the third ventricle—the corpora quadrigemina and the pineal body—are represented by a negative reaction, while all its frontal, superior and lateral structures gave strong reactions that indicate their involvement possibly from pressure Some time after this test the patient had a left temporal decompression performed, and since then developed signs indicating tumor in the right hemisphere

CASE 21.—M. K. Cook County Hospital Oct. 23 1917. Service of Dr. J. Grinker. Clinical diagnosis, tumor or abscess of the cerebellopontine angle. This clinical diagnosis was known to me when this test was made.

Thirty-eight different tissues were used. The five weak reactions in the cortex (Table I) are in apparently no direct relation to each other and exclude the idea of a cortical lesion, but the strong reaction (3 plus) with corpus calosum (III₁) suggests that those reactions are bilateral. The basal ganglia, with the sole exception of the pineal gland, were negative. Thus the remaining positively reacting structure—the pons (III₂)—must be the seat of the lesion while the 3 plus with the choroid plexus (III₃) indicates probably increased intracranial pressure which led to the clinical diagnosis of brain tumor. The clinical localization in the cerebellopontine angle was based chiefly on the involvement of cranial nerves from III and XII. The necropsy performed on Nov. 10 1917 by Dr. J. Nuzum showed pressure on the pons by a large tumor from the nasopharynx.

CASE 22.—Mrs. G. Oct. 22 1917. Michael Reese Hospital Chicago. Dr. S. Kuhn. Clinical diagnosis brain tumor. Thirty-eight different substrates used. The whole aspect of the reaction points to two areas of possible lesion—the frontal lobe and the corpora quadrigemina. If we consider the lesion in the frontal convolution, then it would be expected that the corpora quadrigemina would be involved too through the degeneration of corresponding association fibers while if the primary lesion were to be in the corpora quadrigemina the reaction with the chiasm (III₁) would naturally have to be stronger than found. In addition, the prevalence of strong reactions alone points to the localization of the lesion being in the frontal lobe probably the posterior part of the second frontal convolution.

After receiving this serologic localization Dr. Kuhn disclosed his clinical findings which led him to the localization of the tumor in the second frontal convolution.

CASE 23.—H. G. Oct. 23 1917. Cook County Hospital. Dr. G. W. Hall. Clinical diagnosis brain tumor. The number of positive reactions in the sub-cortical regions suggested the making of an attempt to localize the tumor outside of the hemispheres. On account of that, the fibers running from all cortical areas showing positive reactions were traced. The first thing which attracts the attention is the involvement of the cortical origin of the central path of cranial nerves III and XII (with the exception of the accessorius), the cortical origin of nerves V and XII is located in the lower two-thirds of the anterior central gyrus and is here represented by positive reactions (I₁ and I₂), while the oculomotor and trochlear originate in the superior portion of the second frontal convolution which gave a 3 plus reaction (I₃). The nuclei of all these nerves give a positive reaction (III₁) and it is to be remembered that the nuclei of the third and fourth cranial nerves lie nearest to the walls of the fourth ventricle and that they derive from a cortical area giving a 3 plus reaction; the corpora quadrigemina are 2 plus positive, and the centrifugal fibers from the temporal (I₄) and occipital lobe (I₅) run through the posterior commissure, the nearest structure to the corpora quadrigemina—the choroid plexus (III₃), the cerebellar gray matter (IV₁) and the dentate nucleus (IV₂) all gave a very distinct positive reaction.

On the basis of this analysis the lesion was localized in the fourth ventricle, with the involvement of the dentate nucleus and the gray matter of the cerebellum, of the aqueduct of Sylvius and of the corpora quadrigemina as far as the pineal gland. A possibility of a second focus in the hypophysis was pointed out (IV₃).

The clinical diagnosis was (as disclosed after the tests were reported) tumor in the region of the lower temporal lobe of the right side, with pressure involving the corpora quadrigemina.

The necropsy performed Oct 26, 1917, by Dr J Nuzum revealed a large soft glioma beginning in the dentate nucleus, and extending over the corpora quadrigemina. The hypophysis was undermined by a cyst.

CASE 24—Mr X. Nov 9, 1917. Private patient of Dr B G Hassin. Diagnosis, well localized brain lesion. The result of the test (Table 1) made with thirty-six different substrates did not admit of any other diagnosis than that of a lesion in the upper motor area (I₁₊₄). The clinical diagnosis, received as usual after the delivery of the serologic report, was Jacksonian epilepsy confined to the left leg only, due to an old skull trauma.

CASE 25—Mr XX. Nov 16, 1917. Private patient of Dr A Heym. Diagnosis, epilepsy possibly due to a localized lesion. Thirty-seven different substrates used. The test shows besides rather weak reactions in the parietal and temporal lobes a very strong reaction (3 plus) over the whole extent of the anterior central convolution (I₁₊₂) and the paracentral gyrus (II₂).

The strong positive reactions with the caudate nucleus and corpus mammillare (3 plus—III₁, IV₁) are explained by the fact that the fasciculus subcallosus, which originates in the anterior central convolution, is interrupted in the caudate nucleus, while the central cortical path of the tegmentum, which originates in the same cortical area, after crossing the caudate and lentiform nuclei passes into the neighborhood of the corpus mammillare.

On the basis of the serologic findings the lesion was localized in the upper part of the central convolution. An operation performed ten days later revealed a deep tumor of the size of a hazelnut, which could be easily palpated in this location.

In this brief report the discussion of the individual cases has been purposely omitted and only the most important and striking features have been noted. On the basis of the findings in the limited series, the serologic diagnosis is supported in four cases by the post mortem findings, in two cases by an operation, and in fifteen cases the serologic findings are in complete agreement with definite clinical evidence. Two cases differ from the clinical diagnosis, but the diagnosis has not been controlled by necropsy or operation. In one case (Case 11) the necropsy findings proved that the serologic diagnosis was erroneous.

THE TREATMENT OF GENERAL PARESIS †

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AND

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The first question to be decided in describing the treatment of general paresis is that of the diagnosis. In this clinic we subdivide neurosyphilis into two main types, the mesoblastic and the parenchymatous, thus making the anatomic lesion coincide more or less with the clinical picture.

The mesoblastic type of neurosyphilis is again subdivided into the endarteritic, the meningitic, and the gummatous forms. Since it is not our intention to describe the treatment of these particular forms, we content ourselves with merely mentioning them.

Parenchymatous syphilis of the central nervous system is differentiated, first, according to the location of the lesion, and secondly, according to the clinical picture. Thus, we distinguish between tabes and general paresis, and can further speak of a diffuse cerebral, a focal cerebral, a cerebellar and a tabetic type of the latter disease. We can also speak of a simple dementing type, an expansive type, a type with depressive symptoms in the foreground, etc.

This is quite clear whenever we deal with outspoken clinical pictures, but in incipient paresis, diagnosed mainly by the laboratory findings, the great question arises. When shall we consider a patient having a positive Wassermann in the blood and spinal fluid, a paretic gold curve, a high cell count and positive globulin tests, as a case of general paresis? All this involves fine anatomic differentiation, and, what is more, a coupling of this differentiation with the serologic findings. With the present state of our knowledge we are unable to say, with any degree of accuracy, when a possibly vague cerebrospinal involvement becomes clearly parenchymatous, and whether this corresponds to the time when the serologic tests become the same as those of outspoken general paresis.

For the purpose of this report we will class as paretics all those patients who have the serologic findings of the disease and show any mental symptoms whatever. We feel that we are justified in doing this, for it has been our experience that there is not a single psychotic

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manifestation which cannot be simulated by general paresis. Thus, we have seen a patient in what was at first glance an acute catatonic condition, who had neither neurologic nor physical findings characteristic of general paresis, but who nevertheless showed positive serologic tests. That this patient, William Brown,¹ a summary of whose case appears toward the end of our report, was really a paretic, was proved by subsequent developments. Again, we have frequently seen incipient cases whose complaints are mostly neurasthenic and hypochondriacal. We believe that too much stress cannot be placed on these subjective feelings and wish to emphasize the necessity of observing minor and apparently unimportant neurologic conditions, as well as the necessity of looking for the so-called "fraying of the personality," in such instances. The condition of a patient may not present anything strikingly abnormal to the examiner, yet when carefully interrogated, the relatives or friends may furnish conclusive proof of a gradual decrease of the patient's efficiency and a diminution of his initiative.

Three of the cases reported are essentially tabes with primary optic atrophy. The patients had practically no mental symptoms, except depressions reactive to the realization of their condition.

Syphilitic optic atrophy, an atrophy of the nerve-head, itself a continuation of the cerebral parenchyma, would seem so closely allied to a degeneration of this parenchyma that we feel we are not going too far afield in including such cases in our series. We realize that the blindness tends to localize and neutralize the progressive degenerative factors. We have taken into account this empirically well-known clinical fact, in deciding whether or not the patient was improved.

At this juncture we should like to describe our laboratory technic briefly. Cell count, Pandy and Ross-Jones tests, are too well known to merit restatement. The Wassermann was run with the usual technic, using the antigens described by one of us.² The colloidal gold solution was standardized according to the technic of Miller, Brush, Hammers and Felton.³ We might remark that we agree with Felton⁴ in believing this test to be the result of a quantitative interrelation of the globulin and albumin of the spinal fluid. Not a single spinal fluid giving a paretic curve was observed among the two thousand fluids examined thus far, which gave negative globulin tests. We have been able to produce solutions of globulin manufactured from paretic as well as "luetetic zone" and meningitic spinal fluids. All such solutions give typical paretic curves.

1 All names are fictitious, and are chosen to indicate race or descent.

2 Neymann and Gager. *Jour Immunol*, 1917, **2**, 573.

3 Miller, Brush, Hammers and Felton. *Bull Johns Hopkins Hosp*, 1915, **26**, 391.

4 Felton. *Tr Am Med Assn*, 1917, p 73.

Not an inconsiderable number of the paretic patients examined show negative blood Wassermann reactions, namely, twenty-nine out of a total of 126, or 23 per cent. A few of these were afterwards controlled by the Hecht-Weinberg-Gradwohl modification⁵ and about 50 per cent were positive. It is therefore evident that the widespread idea of a necessarily positive blood Wassermann in general paresis is a chimera.

We will now describe twenty-four cases treated by various methods, partly on account of special exigencies of the individual cases, partly because we wished to draw our own conclusions as to the best form of therapy (Tables 1 to 10, summarized and classified as to results of treatment in Table 11.)

At present the following forms of therapy are used.

The long-established mercury treatment combined with potassium iodid may be discarded as used alone. It is, however, recommended by practically all clinicians as a valuable aid to the other forms of therapy.

Next to this in simplicity is the intravenous treatment. This may sometimes produce results, as is best shown in the case of Mary Olafson, Table 1. We gave this patient, whose weight was but 102 pounds, fifteen intravenous treatments, a total of 7.3 gm. in eight weeks. We thought we had found a simple and adequate way of influencing the serologic findings in the spinal fluid. These ideas were dispelled when we applied the same method to another patient, Leonard Benson, Table 2, an incipient case, who showed fraying of the personality and who reacted to intraspinal salvarsanized serum,⁶ with perineal parasthesias, and to biweekly injections of the diarsenol brand of arsphenamin with an acute arsenical neuritis, in addition to a slight arsenical rash. Perhaps the use of this preparation, which we have come to view as a more toxic preparation than the arsenobenzol brand of arsphenamin or the salvarsan brand, was at fault, more likely, however, the patient was a victim of hypertherapy. We believe that intravenous arsphenamin or its substitutes may help certain cases, but that the danger point is too near the optimum therapeutic.

The resistance of the choroid plexus and the meningeal blood vessels to the passage of arsphenamin and other chemical compounds of complex molecular structure has been demonstrated by McIntosh and Fildes⁷ and others. One must take these organs by storm, so to speak, before one can hope to reach the *Spirochaete pallidae* buried in the depths of the cortex.

⁵ Gradwohl Jour Am Med Assn, 1917, 68, 514

⁶ Serum obtained after intravenous treatment with arsphenamin or any of its substitutes is denoted as arsphenaminized serum.

⁷ McIntosh and Fildes Brain, 1916, 39, 478

Intraspinous therapy with arsphenamized serum is undoubtedly useful, but we believe that the same objections apply to it as to the intravenous treatment, unless one wishes to use the usual Swift-Ellis procedure⁸ and the modification of Ogilvie,⁹ alternately once a week. If arsphenamized serum is given every seven days in the manner described, great care must be taken to avoid bladder, rectal and other root disturbances. We have seen serious disturbances of this nature in no less than six of our patients. In three, the symptoms were transitory and the patients finally recovered complete control of their muscles, with three the results were exceedingly regrettable, in that one developed a permanent and almost complete paraplegia, while the other two remained incontinent. This factor is not to be lightly gone over and is a danger that is always present. A patient may react well to five or six treatments and show subjective or objective bladder disturbances with the seventh. J W Brooks, Table 3, the above mentioned paraplegic, amply illustrates this phase. The serologic improvement is apparent, and coincides with the arrest of deterioration. Were it not for the root disturbances the disease would probably have been arrested after further treatment. We have observed such more or less permanent motor root disturbances, as well as perineal and sacral anesthetics and parasthetics, after intraspinous mercurialized serum.

The reactions which one gets with mercurialized serum, prepared according to the Byrnes method¹⁰ are entirely different. Here the immediate reactions are much more severe, yet, as stated, we have never seen a permanent injury to the muscular or sensory innervation. We believe, however, that little can be accomplished tending toward arresting the disease and changing the serologic findings by the use of this method alone. John Hogan, Table 4, who received thirteen intraspinous mercurialized serum injections, totalling over one third of a grain of mercuric chlorid, will best illustrate this point. Deterioration and death were not prevented. The serologic tests were not influenced. Here we gave the maximum doses of one twenty-fifth of a grain. We do not consider this high dosage as the most efficacious one for general use. The reactions with most patients are far too severe. There really is an enormous amount of irritation, causing high temperatures, extreme pain, meningismus, nausea, etc. We feel that a maximum amount of intensive treatment should and must be given, yet that this must not interfere to such an extent with the patient's general health that it will lower his resistance.

The intraventricular treatment of Hammond and Sharpe¹¹ and the

8 Swift and Ellis. *New York Med Jour*, 1912, **96**, 53.

9 Ogilvie. *Am Jour Syphilis*, 1917, **1**, 509.

10 Byrnes. *Jour Am Med Assn*, 1914, **63**, 2162.

11 Hammond and Sharpe. *Jour Am Med Assn*, 1915, **65**, 2147.

TABLE 1—RECORD OF TREATMENTS

Mary Olafson, aged 22 Ward E2, E1 Admitted Jan 11, 1917 Discharged March 8, 1917

Date	Intra- venous Arsphen- amin	Intra- spinous S Serum, C e	Intra- spinous M Serum	Blood Wassermann Antigen			C Spinal Fluid Wassermann Antigen									Cells per C mm	Globulin		Colloidal Gold Reaction	Reac- tion	Remarks		
							A			B			C				Ross Jones	Pandy					
				A	B	C	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0								
1/16				4*	4	4	4				4				4			93	+	+	5555554320		
1/18	0.3			4	4	4																SI	
1/21	0.5			4	4	4																0	
1/23	0.4			3	1	0																0	
1/28	0.5			4	4	4																0	
1/31	0.5			4	4	4	4				4				4			39				0	Bloody fluid
2/ 4	0.5			1	4	4																0	
2/ 7	0.5			4	4	4	4				4				4			13	(+)	+	5555552000	0	
2/12	0.5			4	4	3																SI	
2/15	0.5			4	4	4																++	
2/20	0.5			2	1	1	4				4				4			10	(+)	(+)	544320000	0	
2/24	0.5			0	1	0																0	
2/27	0.5			0	1	1																SI	
3/ 7	0.6			0	1	1	2				2	4	4	3								+	Bloody fluid
3/15	0.5			0	0	0																0	
3/17	0.5			0	0	0																SI	
3/27							2				4	4	4	4				N C	(+)	+	4433331000		

* In this and the following tables 4 means 100 per cent fixation, 3 means 75 per cent fixation, 2 means 50 per cent fixation, etc

TABLE 2—RECORD OF TREATMENTS

Leonard Benson, aged 51 Ward W3 Admitted Dec 13, 1916 Discharged April 16, 1917

Date	Intra- venous Arsphen- amin	Intra- spinous S Serum, C e	Intra- spinous M Serum	Blood Wassermann Antigen			C Spin d Fluid Wassermann Antigen									Cells per C mm	Globulin		Colloid d Gold Reaction	Reac- tion	Remarks
							A			B			C				Ross Jones	Pandy			
				A	B	C	0 25	0 5	1 0	0 25	0 5	1 0	0 25	0 5	1 0						
12/15				+	+	+															
12/20	0 2						+			+			+			70	++	+++	5555541210	0	Tonsillitis
12/28	0 5	24		+	+	+	+			+			+			78	+++	+++	5555543321	0	
1/ 4	0 6			+	+	+														0	
1/15	0 6																			SI	
1/18	0 6	22		+	+	+	+			+			+			22	++	+++	5555543210	0	
1/25	0 6	15		+	+	+	+			+			+			7	++	+++	555555331	0	
2/ 1	0 6	24		+	+	+	+			+			+			17	+++	+++	5555553300	0	
2/ 8	0 6	24		+	+	+	+			+			+			19	++	+++	5555554320	+	
2/15	0 6	23		+	+	+	+			+			+			14	++	+++	55555413100	+	
2/20	0 6			+	+	+														0	Incontinence
2/23	0 5			+	+	+														0	
2/27	0 6			+	+	+														+	
3/ 3	0 6			+	+	+														0	
3/ 7	0 6			+	+	+														0	
3/10	0 5			+	+	+														0	
3/14	0 6			+	+	+														0	
3/23							+			+			+			8	+	++	5555542100	+	Slight arsenic rash arsenical neuritis

TABLE 3—RECORD OF TREATMENTS

J W Brooks, aged 50 Ward W2, W1 Admitted Aug 16, 1916 Discharged Nov 2, 1917

Date	Intra-venous Asphen-amin	Intra-splinous S Serum, O c	Intra-splinous M Serum	Blood Wassermann Antigen			C Spinal Fluid Wassermann Antigen									Cells per C mm	Globulin		Colloidal Gold Reaction	Reaction	Remarks
				A	B	C	A			B			C				Ross Jones	Pandy			
							0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
8/22				0	1	0	1			1			1			51	1 1	1 1 1	5555513210		
8/21	0.2																			SI	
8/30			1/100																	+	
9/ 9	0.6	25		0	0	0	1			1			1							1	Bloody fluid
9/15			1/50				1			1			1							1	Bloody fluid
9/21	0.6	21		0	1	0	1			1			1			58	1 1 1	1 1 1	5555555321	1	
9/29			1/50				1			1			1			31	1 1 1	1 1 1	5555551200	1	
10/ 5	0.6	22		0	0	0	1			1			3			20	1 1	1 1	5555555110	0	
10/12			1/100				1			1			1			15	1 1	1 1	5555555120	SI	
10/19	0.6	22		0	0	0	1			1			1			19	1 1	1 1 1	1551132100	0	
10/26			1/50	0	0	0	1			1			1			17	1 1	1 1 1	3111111310	1	
11/ 1	0.6	27		0	0	0	1			1			1			15	1 1 1	1 1 1	1553122000	0	
11/ 9	0.6	35		0	0	0	1			1			1			11	1 1	1	1111321000	1 1 1 1	Gradually developing incontinence and paraplegia
12/ 5							2			1			2			11					
9/ 3				0	1	0	1			1			1			10			2221112200		

TABLE 4—RECORD OF TREATMENTS

John Hogan, aged 51 Ward W 3, 2, 1 Admitted Dec 19, 1916 Discharged June 11, 1917

Date	Intra venous Arsphen amin	Intra spinous S Serum, C e	Intra spinous M Serum	Blood Wassermann Antigen			C Spin al Fluid Wassermann Antigen									Cells per C mm	Globulin		Colloid al Gold Reaction	Reac tion	Remarks	
				A	B	C	A			B			C				Ross Jones	Pandy				
							0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0							
12/22	0.2			4	1	4	4			1			1			61	+	++	5555513210		Bloody fluid	
12/28			4	4	4																	
1/18		1/400			1			1			1			1				+++	+++	555555531		0
1/25		1/100			1			1			1			1		29	+++	+++	555555531	0		
1/31		1/75			1			1			1			1		38	+++	+++	5555554131	SI		
2/ 7		1/50			1			1			1			1		30	+	++	5555555500	++		
2/15		1/50			1			1			1			1		21	+++	+++	5555554320	SI		
2/20		1/50			1			1			1			1		21	+++	+++	5555555120	SI		
3/ 1			1/37				1			1			1		21	+	++	5555554310	SI	Bloody fluid		
3/ 7	0.3		1/37	4	4	4	1			1			1								SI	
3/15			1/25				1			1			1		11	+++	+++	5555555521	SI			
3/22			1/25				1			1			1		13	+++	+++	5555551100	SI			
3/29			1/25				1			1			1		31	++	+++	5555555421	SI			
4/ 5			1/25				1			1			1								SI	
4/12	0.5		1/25	2	4	2	4			1			1		26	++	++	5555554210	SI		Patient steadily de teriorated Died in a state hospi tal 2 months later	
6/11				1	1	3	4			1			1									

TABLE 5—RECORD OF TREATMENTS

Wilhelm Sturdivant, aged 36 Ward W 2, 3 Admitted May 31, 1916 Discharged Oct 23, 1916

Date	Intra-venous Arspen-amin	Intra-splinous S Serum, O c	Intra-splinous M Serum	Blood Wassermann Antigen			O Spinal Fluid Wassermann Antigen									Cells per C mm	Globulin		Colloid u Gold Reaction	Reaction	Remarks		
				A	B	C	A			B			C				Ross Jones	Pandy					
							0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0								
6/ 2				4	4	4	4				1				1			6	++	++	553553320		
6/ 3	0.4																					0	
6/ 8	0.6	10		4	4	1	4				4				1			6	+++	+++	553553210	0	
6/14			1/100				4				4				1			10	+	+++	553553211	SI	
6/22	0.6	15		4	4	4	4				4				4			7	++	++	5535542000	0	
6/30			1/50				4				4				4			10	+	+++	5534321000	SI	
7/ 6	0.6	25		4	1	1	4				4				4			38	+	+++	5514331100	0	
7/13	0.6	28		4	4	4	4				4				4							SI	Bloody fluid
7/19	0.6	23		4	4	4	1				4				4			63	+	++	5511431000	0	
7/27	0.6	25		4	4	4	4				4				1			7	+	++	1535513210	++	
8/ 3	0.6	16		4	4	4	4				4				4			8	+	++	4545543100	0	
8/10	0.5	21		4	4	4	4				4				4			3	+	++	1144131000	0	
8/17	0.5	20		4	4	4	4				4				4			2	+	++	5534321110	0	
8/24	0.6	10					4				4				4			N C	+	++	4113322100	0	
8/30			1/30																			0	
9/ 9	0.6	10		3	4	4	4				4				4			N C	+	+	4411431100	0	
9/15			1/50				4				4				4			18	+	++	5511443210	0	
9/21	0.6	18		4	1	1	4				4				3							+	Bloody fluid
9/29			1/50				4				1				4			5	+	+	3535531000	++	
10/ 5	0.6	22		4	4	4	1				1				1			10	+	++	555554321	0	
10/12			1/50				1				4				4			7	++	++	553555500	SI	
10/19	0.6	10		4	4	4	4				2				3			7	+	++	2333321000	0	Discharged
12/ 5				4	1	1	1				4				4			5	(+)	(+)	2222533300		Second admission, Jan 6, 1917
1/11	0.3	25		4	1	4	1				2	4	4	0				3	(+)	+	1112222000	0	
1/18			1/50				0				3				0			4	(+)	+	2224542000	+	
1/25			1/30				0				1	4	1	0				14	(+)	+	1211514100	SI	
2/ 1	0.3			4	4	1																0	
2/ 2			1/30				1				3	4	4	0				2	(+)	(+)	222221000	+	
2/ 8			1/50															11	+	+	2333113200	+	Anticomplementary
2/15	0.2			1	4	4	0				0	3	4	0				4	+	++	2231110000	0	
2/20			1/50				1				1	4	1	0				3	0	(+)	1415333210	SI	Discharged Feb 23, 1917. Ambulant treatments follow
3/ 3	0.3	22		1	1	3	0				0	0	4	0			N C	(+)	(+)	1112210000	0		
3/10	0.5	20		3	4	3	0				0	4	4	0				12	+	+	1113331000	0	
3/17	0.6			3	1	3																0	Slight incontinence
5/25				4	1	4	0				1	3	1	0			N C	+	+	2222200000		Attempted suicide April 25, 1917. Re moved to sanitarium	
9/21				1	1	0	1				0	1	3	0				5	0	0	1123332000		
1918																							
1/22				2	2	1	0				0	1	1	0				2	(+)	(+)	1123310000		Patient no longer shows bladder dis.

TABLE 8—RECORD OF TREATMENTS

James Kelly, aged 45 Ward W3 Admitted Sept 2, 1915 Discharged Oct 22, 1915

Date	Intra- venous Arsphen- amin	Intra- spinous S Serum, C c	Intra- spinous M Serum	Blood Wassermann Antigen			C Spinal Fluid Wassermann Antigen									Cells per C mm	Globulin		Colloid 11 Gold Re action	Reac- tion	Remarks
				A	B	C	A			B			C				Ross Jones	Pandy			
							0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0						
9/ 3				0	0	0	4			3			2			8	+	+	5554132100		Anticomplementary
9/ 8	0.5																			0	
9/13	0.6	20					3			4			2			10	+	+	3111121000	0	
9/22	0.6	10														11	+	+	4411332100	0	
9/29	0.6	10		0	0	0	0			0			0			1	+	+	4113311100	0	
10/ 6	0.6	20					0	2		0			0			8	+	+	2220221000	0	
10/13	0.6	20					0	0		0			0			9	(+)	(+)	222222210	0	
10/20	0.6	20		0	0	0	0	1		0	3		0	1		3	(+)	(+)		0	

TABLE 9.—RECORD OF TREATMENTS

Mabel Andrews, aged 17 Wt 124 lb Admitted April 3, 1918 Discharged May 24, 1918

Date	Intra-venous Asphen-anti	Intra-splenic S. Serum, Cc	Intra-splenic M. Serum	Blood Wassermann Antigen			O Spinal Fluid Wassermann Antigen									Cells per Cmm	Globulin		Colloidal Gold Reaction	Reaction	Remarks
							A			H			O				Roe-Jones	Pandy			
				A	H	O	0.5%	0.5	1.0	0.5%	0.5	1.0	0.5%	0.5	1.0						
4/ 7	1	1	1	0				0	1		0		21	1	1	15553/100		
4/11	0.0	15	.	.			1	.			1			1	.	11	1	1	31113/1000	SI	
4/21	1/50		..		0				0	1		0						SI	Bloody fluid
5/ 4	0.0	25	.	1	1	1	0				1	1	1	0		11	1	1	22113/1000	1-1	
5/10	0.1	18					0				0	0	1	0		8	1	1	11233/1100	SI	
5/17		1/50				0				0	0	0	0		8	1	1	11233/1100	1	Discharged Second admission June 21, 1918
6/22	0.5	21		1	1	1	1				0	1	1	1		3	0	(1)	91333/1000	SI	
6/30	.	.	1/50				0				0	1	3	0		5	(1)	1	11133/1000	SI	
7/ 0	0.0	25		1	1	1	3				1	1	1	3		7	(1)	1	11133/10000	SI	
7/13		.	1/50				0		.		0	1	1	0		3	0	(1)	11133/1100	SI	
7/20	0.0	31		3	1	1	0				1	1	1	1		12	(1)	(1)	11133/10000	SI	
7/27	0.0	21		1	1	1	0		..		0	1	1	0		1	(1)	1	11133/1100	SI	Discharged July 31 Readmitted Aug. 3, 1918
8/ 3	0.0			1	1	1															Discharged Aug. 9, 1918 Final report submitted from an other clinic
1017 10/22				1	1	1	0				0	..		0		1	0	0	00000000000		

Date	Intra venous Arsphen amin	Intra spinous S Serum C c	Intra spinous M Serum	Blood Wassermann Antigen			O Spinal Fluid Wassermann Antigen									Cells per O mm	Globulin		Colloidal Gold Re tention	Reac tion	Remarks	
				A	B	C	A			B			C				Ross Jones	Pandy				
							0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0							
1/23							0				2	1	1	0			17	+	+	555555130		Dispensary reports
2/ 2	0.3				3																0	
2/ 9	0.3				0																0	
2/16	0.3				0																0	
2/23	0.3				0																0	
3/ 2	0.3				0																0	
3/ 9	0.3				0																0	
3/16	0.3				0																0	
3/23	0.3				0																0	
3/28	0.3				0																0	
3/30	0.3				0																0	
4/ 3	0.3				0																0	
4/10	0.3				0																0	
4/13	0.3				0																0	
4/17	0.3				0																0	
5/ 1				1	4	1															0	Admitted April 27, 1917
5/ 2	0.6			1	1	2	0			0	1	1	0			5	+	++	5555111000	SI		
5/ 9	0.6			1	3	0															SI	
5/16	0.5			1	1	1															SI	
5/18		22					0			0	0		0			5	+	+	555542100	SI		
5/23			1/200																		SI	
5/30	0.6			1	3	0	0			0	0	2	0			6	++	++	555553100	SI	Anticomplementary bloody fluid	
6/ 8			1/50				0			0	3	1	0			5	+	+	555542100			
6/15	0.6	18					0			0	0	3	0								SI	Bloody fluid
6/23			1/50				0			0	0	1	0			8	+	+	455553222		0	
6/29	0.6	22		1	4	0	0			0	1	1	0			5	+	++	555543200		+	
7/12	0.3		1/50	0	0	0	0			0	1	3	0			6	+	+	555541000	SI		
7/23	0.1	25		0	0	0	0			0	0	0	0			10	++	++	1555531000	SI		

TABLE 11—DATA AND CLASSIFICATION OF AUTHORS' CASES

PROBABLY ARRESTED					
No	Name	Diagnosis	Present Clinical Status and Occupation	Serologic Tests after Treatment	Duration of Present State
1	Wilhelm Sturdivant	General paresis, cerebral type	Well, but in a sanitarium	Practically negative	12 months
2	William Brown	General paresis, cerebral type	Well, butcher	Practically negative	15 months
3	Isaac Goldberg	General paresis, cerebral type	Well, tailor	Practically negative	14 months
4	James Kelly	General paresis, focal type	Well, bookmaker	Practically negative	27 months
5	Mabel Andrews	Cerebrospinal lues	Well, household duties	Practically negative	17 months
6	Mary Hitzel	General paresis, focal type	Well, household duties	Negative, except atypical gold curve	6 months
IMPROVED					
7	Mary Olafson	Cerebrospinal lues, probably general paresis	Whereabouts unknown	Improved	?
8	Tina Burroughs	General paresis, cerebral type	At home	Unchanged	Being treated
9	Richard Smith	Taboparesis	Undergoing further treatment	Unchanged	Being treated
10	Charles Green	Taboparesis and primary optic atrophy	At work, clerk	Unchanged	7 months
11	Samuel Rich	Taboparesis and primary optic atrophy	At work, actor	Unchanged	7 months
12	Carl Listerman	Tabes with 8th nerve involvement	At home, works	Improved	9 months
UNIMPROVED					
13	John Hogan	General paresis, cerebral type	Died	Unchanged	
14	Harry Blumenstein	General paresis, cerebral type	At work, clerk	Unchanged	
15	Fred O'Shay	General paresis, cerebral type	In state hospital	Unchanged	
16	Thomas Black	Taboparesis and primary optic atrophy	At home, in charge of nurse	Unchanged	
17	Frank O'Neil	General paresis, cerebral type	Died	Unchanged	
18	Thomas Sutton	General paresis, focal type	At home, in care of family	Unchanged	
HARMED					
10	J W Brooks	General paresis, cerebral type	Paraplegia, in state hospital	Slightly improved	
20	Ralph Fisher	General paresis, cerebral type	Died, July 4, 1917	Unchanged	
21	Sidney McIntosh	General paresis, cerebral type	Incontinent, in state hospital	Unchanged	
22	Leonard Benson	General paresis, cerebral type	At home arsenic neuritis	Unchanged	
23	Albert Haupt	Taboparesis and primary optic atrophy	Died, acute arsenic poisoning	Improved	
24	John Suderman	General paresis, cerebral type	Died in a convulsion six days after a treatment	Unchanged	

intradural Cotton¹² methods are undoubtedly very praiseworthy. The flow of the spinal fluid, as has been shown by Weed,¹³ is toward the foramen of Magendie, starting from the ventricles and from the spinal canal. A therapy embracing these anatomic-physiologic considerations is therefore the most rational. Yet our patients, fairly early cases, dread the necessary surgical procedures, besides we agree with Cotton¹² who says "Given an early case of paresis we would say that the Swift-Ellis method was as efficient as any." We furthermore believe that early cases are the only ones which can be arrested, and that even could a more advanced case be arrested, the result achieved would be regrettable from the social aspect. We have arrested one such case, Wilhelm Sturdivant (Table 5). The history follows.

CASE 1—Wilhelm Sturdivant, aged 36, accountant, admitted May 31, 1916

Date of Infection—Chancre 1902, without secondaries, sporadic treatment, mercury by mouth

Life History—Excellent educational opportunities, married in 1908, happy marriage, two children, no miscarriages, efficient in business

Onset of Psychosis—Marked irritability in spring of 1912, easily provoked, homicidal episode. There was no marked change until 1915, when he became rather inefficient and had to give up his work and loafed around, trip to Europe on account of nervousness, no improvement. January, 1916, he attempted to work in a bank but had to give up the position in March, 1916, on account of eye trouble and general inefficiency. An examination disclosed a left Argyll Robertson pupil. At this time he was sent to a state hospital, where he remained until his admission to this Clinic, May 31, 1916.

Status on Admission—Rather agreeable, euphoric in regard to his illness, lack of judgment, was prone to hold long-winded pointless conversations, slurring speech, left Argyll Robertson pupil, right pupil sluggish, marked ataxia, tremor of tongue, knee and ankle jerks absent on both sides, anesthesia of both legs below the level of iliac crests, for serologic findings, see Table 5.

Diagnosis—Taboparesis (moderately advanced)

Progress During Treatment—Showed no signs of irritability, sent home on Oct 23, 1916, where he remained in about the same condition, but had a tendency to meddle in household affairs. Readmitted for further treatment Jan 6, 1917. Speech had markedly improved, general attitude had remained the same. Sent home again Feb 23, 1917. Ambulatory treatment was given until March 17, 1917, then treatment was stopped because the spinal fluid became almost negative and the patient developed slight bladder symptoms. The patient tried to hold several positions, but was discharged for his inefficiency. April 25, 1917, he attempted suicide by gashing his throat with a razor, because he realized that he would not be able to hold a position commensurate with his social standing. He was sent to a private institution, where he has done fairly efficient work under guidance. No more bladder disturbances. His mental condition remained stationary up to the time of this report.

Thus we see a rather advanced, arrested case, in which the patient is now a burden to himself and family.

Wilhelm Sturdivant was not treated according to what later became our routine procedure, that is, once a week with either intravenous

12 Cotton. *Am Jour Insan*, 1915 and 1916, **72**, 125, 355 and 485

13 Weed. *Jour Med Research*, 1914, **31**, 21, 51 and 93

arsphenamin and intraspinous arsphenamized serum, or with mercurialized serum. The details of this routine are given below.

After the diagnosis is established, the patient is put on a routine course of mercurial inunctions and potassium iodid by mouth. Careful attention is paid to mouth hygiene during the entire period of treatment. We give these inunctions six days a week and a hot bath on the seventh day, and give a saturated solution of potassium iodid beginning with 15 drops three times a day, and increasing one drop a day until the maximum of 150 drops a day is reached. Usually furunculosis is noticed before this time, thereupon the iodid is discontinued for about a week, to be later recommenced at 15 drops three times a day.

Arsphenamin is given intravenously, beginning with 0.2 or 0.3 gm., according to the body weight of the patient. If the patient reacts badly to this initial dose, all treatment is discontinued and we make no further attempt to treat him. We consider as serious reactions any signs of arsenical rash, neuritis, albuminuria, and marked circulatory disturbances, that is, syncopal attacks.

The next week the patient is given 0.5 or 0.6 gm. of arsphenamin. At the completion of the arsphenamin administration, 50 c.c. of blood are withdrawn into a sterile centrifuge tube, a lumbar puncture is made and the spinal canal is drained.

We are indebted to Dr. Henry A. Cotton for this suggestion, believing, as he and Barbat¹⁴ do, that this procedure partly overcomes the aforementioned resistance of the choroid plexus and meningeal vessels to the drug. It is marvelous how much fluid one can withdraw from the spinal canal of a paretic without causing the slightest discomfort, in fact, the more fluid withdrawn, the less reaction is likely to result. We have withdrawn as much as 80 c.c. at one time.

The next day the blood, which has been allowed to clot in the ice box over night, is centrifuged, poured into a second sterile centrifuge tube, again centrifuged and inactivated in a water bath, at 56 C for half an hour. This overcomes the use of pipets, which, even when plugged with cotton, always involve the danger of salivary contamination.

The third week $\frac{1}{100}$ gram of mercury (Mulford's mercurialized serum) is given intraspinally. Though we know by the work of Besredka¹⁵ that animals can be sensitized to foreign protein by intraspinal injections, we have not found that this particular preparation causes reactions which might be interpreted as anaphylactic.

The fourth week, arsphenamin and arsphenamized serum are again given as described.

14 Barbat Jour Am Med Assn, 1918, 70, 147

15 Besredka Compt rend Soc de biol, 1910, 68, 1110

The fifth week, $\frac{1}{50}$ grain of mercury is introduced in the spinal canal, provided the patient has theretofore shown no unfavorable reaction after the initial dose

From now on the alternate treatment with arsphenamin and intra-spinal mercury proceeds regularly. This is no dogmatic rule. Each patient presents his individual problem and must be treated as a human being, not as a member of a group of cases.

We have arrived at this particular form of treatment from practical as well as theoretical considerations. If we hope to accomplish results, and by results we mean clinical and serologic recoveries, we must use all the antisypilitics at our disposal, being careful not to overdo the therapy as before stated.

Whenever a patient begins to evince signs of debility, it is best to give him a complete rest and discontinue all treatment. Whenever possible and practicable, we send such patients home. After such a rest we were often surprised to find that patients who had shown no improvement during extensive and intensive treatment, suddenly became serologically negative of their own accord. This "recuperation phase" is well shown by William Brown, Table 6. His history follows.

CASE 2—William Brown, aged 29, butcher, admitted March 21, 1916

Date of Infection—Possibly December, 1914, no history of secondaries, sporadic and unreliable treatment

Life History—Passed third grade of public school, married November, 1915, a girl who was three months pregnant by him, unhappy marriage on account of religious difficulties, fairly efficient as a butcher and delivery man.

Onset of Psychosis—December, 1915, the patient was found wandering aimlessly on the street at 3 a. m., could not tell what he was doing and only cried, sat around at home for some time, but later, February, 1916, began to work. March 14, 1916, he refused to eat or talk, stood in one corner of the room for six hours, and wandered aimlessly around the house saying, "I had sixty dollars. Where are they at?" He remained in this condition, eating nothing and speaking only a few words, until his admission to this clinic on March 21, 1916.

Status on Admission—The patient lay quietly in bed, eyes open, seemed to notice people who came into the room but would answer no questions. He had to be tube-fed and catheterized, neurologic and physical status negative except for sluggish oval pupils. Tentative diagnosis, catatonic reaction type. For serologic findings, see Table 6.

Diagnosis—General paresis, cerebral type (early stage)

Progress During Treatment—Tube-fed until March 24, 1916. Then the patient gradually became more and more responsive, treatments having begun March 30, 1916. More or less indifference was manifested until about the middle of April, 1916. From this time on he was normal. He was discharged Aug 1, 1916. Readmitted for further treatment Sept 20, 1916. Serologic findings showed *first improvement*. Discharged Oct 31, 1916. Readmitted Nov 12, 1916. Discharged Nov 26, 1916. Went to work at his old job. Treated sporadically and ambulant until July 23, 1917. Continued to work during this time. At the time of this report he was earning as much money as before his illness and his mental and physical status was quite normal. His pupils were round, regular and reacted promptly to light and accommodation.

Reverting to our twenty-four cases and tabulating them (Table 11), we can divide these patients into four main groups according to the results achieved. Each of these groups embraces six patients, or 25 per cent of the total number.

The patients of the first group are all doing well and all except one, Wilhelm Sturdivant, whose history has already been given, have been discharged from the hospital and are at work. The serologic findings of the spinal fluids of five of them are practically negative, except for slightly positive globulin tests and consequently a slight atypical change in color in the tubes of higher dilution of the colloidal gold. One of them still shows strongly positive globulin tests and consequently an atypical parietic gold curve. The blood Wassermann of two has not become completely negative.

We have found that it is possible to change the serologic findings of most patients who are given the intensive treatment outlined above. Of course this change is not always permanent. It is easiest to reduce the number of cells per cubic millimeter. We have always observed a reduction of the cell count after repeated spinal punctures and thorough drainage of the spinal canal. Consequently, a reduction of the cell count alone, unless at least a month has elapsed since the last puncture, is unimportant. The Wassermann reaction can only be reduced to negative in the spinal fluid after long intensive treatment. It is hopeless to expect a change until at least eight intraspinal treatments have been given. Often there is no change until after the fifteenth or twentieth injection. Therefore, a patient who has not had at least eight intraspinal treatments, at weekly intervals, can be said to have been *inadequately treated*. In successfully treated cases, traces of the luetic amboceptor usually remain, when double and quadruple the quantity of spinal fluid is used without increasing the other biologic reagents, that is, complement, antigen, hemolytic amboceptor and sheep corpuscles. The colloidal gold curve is often changed, in so far that the first tube may show a more or less reddish tinge, similar to the color observed in typical meningitic curves. We do not consider this a true change or improvement, since we have often seen it in patients who have again shown typical parietic curves after a respite from treatment. It is probably due to meningitic irritation, a consequence of the therapy. A true change in the gold curve, such as is shown in five of the six cases of Group 1 (Table 11), can only be obtained after a maximum number of intraspinal treatments. Even then it is not usual for the gold curve to revert to a completely negative reaction. All this is in close conjunction with the positive or slightly positive globulin findings, which are encountered in practically all cases of cerebrospinal lues after treatment. Such a trace of globulin may perhaps be regarded as

an irritation phenomenon, due to permanent changes in the injured parenchyma and mesoblast

We have already given the clinical histories and serologic charts of Wilhelm Sturdivant and William Brown. We will now present those of the remaining four patients in the first group

CASE 3—Isaac Goldberg, aged 43, tailor, admitted May 26, 1916 (Table 7)

Date of Infection—Unknown

Life History—Poorly educated, married in 1898, happy marriage, one miscarriage, six children living, two dead, efficient at his work

Onset of Psychosis—August, 1915, he began to be overtalkative and became forgetful. He was unable to do efficient work, talked about making a lot of money and the possibility of becoming governor of the state, piled the household garbage in heaps on the kitchen floor, attempted suicide by turning on the gas

Status on Admission—Variable swings of mood, but on the whole, placid and euphoric, easily upset by trifles, but soon laughed them away, no insight, speech and writing intact, neurologic status normal, for serologic findings see Table 7

Diagnosis—General paresis, cerebral type (early stage)

Progress During Treatment—Remained in about the same state, with gradually decreasing euphoria and a gradual development of insight. Discharged Aug 29, 1916. Readmitted for further treatment Jan 17, 1917. Complained of headache, and had been unable to hold various jobs. Seemed clinically normal. Discharged Feb 17, 1917. Went to work and from this time on did exceedingly well, earned more money than he had previously, because he learned to do cutting. He had only one ambulant intravenous treatment, since he felt well and was afraid of the pain during and after treatment

This is a treated patient who is back at work and who is not only socially possible, but actually helps support his large family

CASE 4—James Kelly, aged 45, bookmaker and gambler, admitted Sept 2, 1915 (Table 8)

Date of Infection—Chancre in 1888, no treatment, no secondaries

Life History—Moderate education, free and easy life as a gambler and racetrack follower, abnormally free sex life, occasional sprees. Married in 1913, happy marriage, no children

Onset of Psychosis—The patient had an epileptiform convulsion in July, 1913, and was unconscious for about twenty minutes. July, 1914, had another similar attack. Jan 22, 1915, he had a third attack and began taking iodids. July 14, 1915, he had a fourth attack and had an anterograde amnesia for events for a period of two weeks

Status on Admission—Perfectly clear mentally, good grasp on the situation, no memory defect, no speech or writing defect, neurologic status normal, for serologic findings, see Table 8

Diagnosis—General paresis, cerebral type

Progress During Treatment—Continued normal and had no further convulsions, was back at his old work and doing well Dec 1, 1916. He has since been reported as still at work.

CASE 5—Mabel Andrews, aged 42, admitted April 3, 1916 (Table 9)

Date of Infection—Unknown

Life History—Excellent education, married in 1904, happy marriage, no miscarriages; efficient in her household duties

Onset of Psychosis—In 1913 the patient had a condition described by the husband as "blind staggers." No headache but marked dizziness and "saw

double" The attacks lasted a few seconds over a period of two to three weeks At the beginning of February, 1916, the patient became overanxious about an invalid sister Feb 19, 1916, she became dizzy, said her "head felt funny" and that she "was going crazy", wept and asked incessant questions about trivial matters There was an amnesia for these few days of confusion

Status on Admission—Overtalkative and euphoric, memory for dates very poor, retention good, calculation and general information poor, marked lack of personal cleanliness, insight good, speech and writing unimpaired, pupils regular, right pupil markedly sluggish to light, left less so, right knee-kick practically absent, left unimpaired, no sensory changes For serologic findings, see Table 9

Diagnosis—Cerebrospinal lues, probably beginning parenchymatous process

Progress During Treatment—The patient gradually became querulous and depressed, showed marked and unfounded dislike for certain persons Discharged May 29, 1916 Readmitted June 21, 1916 The serologic findings, which had been markedly improved, were again more positive Finally discharged Aug 9, 1916 She was given eight or ten further treatments in another city and was reported as doing well, Oct 22, 1917 All mental symptoms had disappeared and the serologic findings of the spinal fluid were reported negative (Table 9)

There is some doubt whether we are here dealing with a pure case of cerebrospinal syphilis or with a case that shows a beginning parenchymatous involvement As just such cases ought to have the benefit of immediate treatment, we have included her in our series

CASE 6—Mary Hitzel, aged 35, housekeeper for father, admitted April 27, 1917 (Table 10)

Date of Infection—Chancre in the spring of 1908, well marked secondaries two months later, good and regular treatment with mercury for five years, arsphenamin, one dose in 1915 and two doses in July, 1916 Very intensive treatment in the dispensary of this hospital from Feb 2, 1917 (See Table 10)

Life History—Passed fourth grade of public school Married in 1907, unhappy marriage, cruel treatment, syphilitic infection derived from husband, divorced in 1910, efficient housekeeper

Onset of Psychosis—Began feeling drowsy in 1915, headaches and cramp-like pains in body, November, 1916, had paresthesias over whole left side of body and slight ataxia in arms

Status on Admission—Mood unimpaired, no memory defect, retention poor, partial insight, speech stumbling and sticking, both pupils react sluggishly to light, knee and ankle jerks hyperactive, Babinski on right side, hemi-anesthesia of left side of body For serologic findings see Table 10

Diagnosis—General paresis, focal type (early stage)

Progress During Treatment—Patient's mood continued normal, insight improved, paresthesia and anesthesia disappeared entirely, speech unimproved, neurologic findings unchanged, discharged July 26, 1917 The patient reported several times at the dispensary and was doing quite well, attending to her household duties at home

The second group is less satisfactory as far as clinical and serologic results are concerned The case of Mary Olafson (Case 7, Table 11) is typical of the final status The method of treatment is not typical In all other cases it was of the usual kind, as outlined Two cases, Tina Burroughs and Richard Smith (Cases 8 and 9, Table 11), are still undergoing treatment Charles Green and Samuel Rich (Cases 10 and

11) are at work and doing well. Their sight, decreased to about 20/200 as a result of primary optic atrophy, has not grown worse. Carl Listerman (Case 12), with marked tabes and absolute deafness on account of eighth nerve involvement, is doing some work as a huckster and market messenger.

The patients of the third group are clinically and serologically unimproved. John Hogan (Case 13, Table 4), whose serologic chart has been shown, is typical of this group. Harry Blumenstein (Case 14), a clerk, is at work, having been discharged from the hospital with status unchanged. His improvement is probably due to a simple remission.

The last group is very interesting. All these patients have been more or less harmed by the treatment. The status of J W Brooks (Case 19), who gradually developed a paraplegia, after the eleventh intraspinal injection, having previously had ten treatments without serious reactions, remains unchanged. Directly after the injection the patient complained of extreme pain. The next day, following a primary retention of urine, incontinence developed and within a week the control of the anal sphincters was also lost. The patient was able to get out of bed and walk a little three or four days after the treatment, but the strength of the muscles of his legs gradually decreased and after a month had elapsed the paraplegia was almost complete. Later, this condition improved somewhat, but he never walked again. The table illustrating his serologic findings has already been shown (Table 3). Ralph Fisher (Case 20) and Sidney McIntosh (Case 21) became incontinent. The former developed this condition after three intraspinal treatments, the latter after the second treatment. Fisher was subsequently given an intraventricular treatment of 25 c c of arsphenamized serum. This did not arrest the progressive character of the disease and he died five months after admission to the hospital. McIntosh was treated intravenously six times after the development of bladder symptoms. No clinical or serologic changes resulted. He was sent to a state hospital. Leonard Benson (Case 22) developed a marked arsenic neuritis as has already been stated. Albert Haupt (Case 23) first showed a marked arsenic rash, then nephritic symptoms and finally died of arsenic poisoning seventeen days after the seventh intravenous treatment. The blood picture was that of a typical aplastic anemia with extraordinary leukopenia. The necropsy showed typical liver and kidney degenerations. Both patients were treated with the diarsenol brand of arsphenamin, as was another, not included in this series, who also developed an arsenic rash. John Sudermann (Case 24) died in convulsions six days after an intraspinal treatment. This death is probably due to the convulsion, which in turn is probably a simple manifestation of the disease. On the other hand, the possibility

exists that it can be connected with the treatments. For this reason we have included him in our last group.

It is probable that the poor results obtained with the patients of this last group can be partially overcome by the careful use of arsenic preparations other than the diarsenol brand. No further case of arsenic poisoning has occurred. The danger of motor and sensory root disturbances cannot be entirely avoided, yet this difficulty is outweighed by the excellent results obtained with 25 per cent of our patients.

Such results would appear worth while. In reviewing the reports of some of the workers in this field, such as those of Fordyce,¹⁶ Ogilvie,⁹ Walker and Haller,¹⁷ Draper,¹⁸ Stoner,¹⁹ Byrnes,¹⁰ Cotton,¹² Cutting and Mack,²⁰ Riggs and Hammes,²¹ Tilney,²² Gaines,²³ Amsden²⁴ and others, we have found only eight cases of treated general paresis and cerebrospinal syphilis in a total of several hundred, reported serologically negative. Moreover, the majority of these writers believe that it is useless to treat general paresis. We believe that the results obtained by us are due to long-continued intensive treatment, as well as to our special method of application. Furthermore we believe that every case of general paresis, in the early stages of the disease, ought to be given this "fighting chance" of recovery. We feel absolutely certain that the large percentage of clinical recoveries and the serologic results exclude the possibility of the recoveries being due to simple remissions, in the old sense of the word. We are not certain that our patients will remain in their present state indefinitely, but even if all of them should relapse, we feel that our efforts have not been in vain and that the patients and the community have benefited.

SUMMARY

Twenty-four cases of general paresis, treated according to our method, alternately once a week with arsphenamin serum and mercurialized serum are described.

Six patients were so markedly improved that five of them were able to resume their occupations. All of them gave practically negative serologic findings. The average duration of the present status is fifteen months. We consider these are arrested cases.

16 Fordyce Jour Am Med Assn, 1917, **68**, 1482

17 Walker and Haller THE ARCHIVES INT MED, 1916, **18**, 376

18 Draper Jour Am Med Assn, 1916, **66**, 400

19 Stoner Cleveland Med Jour, 1916, **15**, 238

20 Cutting and Mack Jour Am Med Assn, 1914, **62**, 903

21 Riggs and Hammes Jour Am Med Assn, 1914, **62**, 1277, Ibid, 1917, **68**, 194

22 Tilney Long Island Med Jour, 1914, **8**, 122

23 Gaines Jour Georgia Med Assn, 1915 and 1916, **5**, 105

24 Amsden Jour Nerv and Ment Dis, 1916, **43**, 265

Six others were somewhat improved, four resuming their occupations, while two are continuing their treatment. All of these were somewhat improved serologically.

Six showed no clinical or serologic improvement, except in one case. This is undoubtedly a clinical remission, the serologic status remained unchanged.

The last six were harmed by the treatment. One developed a paraplegia, two became incontinent, one died of acute arsenical poisoning and one developed an arsenic neuritis, finally, one died in convulsions, possibly as the result of the treatment.

Whenever the serologic findings tend to become negative, they usually change in the following order and manner:

The cell count is first reduced to normal.

The Wassermann reaction then becomes negative.

The paretic colloidal gold curve changes to an atypical or negative one.

The globulin tests became less marked, but traces of globulin usually remain.

Twenty-three per cent of all the paretic patients examined in this clinic show negative blood Wassermann reactions.

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A STUDY OF EIGHTY CASES OF EMPYEMA AT CAMP UPTON*

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Even a casual observation of the cases of empyema which have appeared in the Base Hospital at Camp Upton during the past winter and spring shows that we are dealing for the most part with an altogether different type of this disease from that to which we are accustomed. The very early appearance of this complication in the course of pneumonia its unusual bacteriology and the very high mortality which accompanies it, even under favorable conditions are the most striking and important variations. Closer study indicates a different train of symptoms certain alterations in physical signs and a modified pathologic picture, while operative procedures which when resorted to in ordinary empyemas give almost uniformly good results, have in this epidemic been attended by so high a death rate as to cause both physician and surgeon to question seriously their advisability, value and type.

In view of these deviations from the usual in this frequent cantonment infection, a close study of all cases was imperative. In this problem it was at once apparent that closely associated laboratory and clinical methods must be constantly applied, and a large portion of the work of the medical and laboratory staffs of this hospital has been devoted during the past winter, to this insistent problem. This study has been a conjoint clinical and laboratory one far more than is usually the case, for it has been found absolutely necessary that the laboratory staff follow the clinical aspects of the cases, even to the point of studying the physical signs and a proper clinical comprehension of the individual case has been found inseparably connected with the work in the laboratory.

Analysis of the clinical picture and the laboratory findings soon showed us that we were dealing with a specific and virulent infection

*Submitted for publication May 18 1918

TABLE 1—DATA OF EMPYEMA CASES

No	Type of Pneumonia	Onset of Empyema	Type of Organism		Blood Culture	Treatment	Termination	Post Mortem Findings
			Sputum	Pleural				
1	Sec Infl	1/10-1/16	Pn II	Pn II		Aspiration	Died 1/17/18	
2	Primary	1/ 9-1/11	Pn I	Pn I		Resection	Recovering	
3	Sec Infl	12/15-1/ 1	Pn I	Pn I		Resection		
4	Sec Infl	12/18-1/ 1	Pn I	Pn I	Neg	Resection	Duty 2/19/18	
5	Sec pleur	3/15-3/22	Pn II	Pn II		Resection	Convalescent	
6	Primary	3/22	Pn II	Pn II		No record	Died 3/26/18	Lobar pn , L U and L R U , emp lt
7		2/ 1-2/22	Pn II	Pn II	Pn II	Thoracotomy	Duty	
8	Sec Infl	3/ 7-1/ 8	Pn IV	Pn IV		Resection	Prognosis (?)	
9	Primary	3/26-3/30	Pn IV	Pn IV		No record	Died 1/3/18	Lobar pn , rt bilat , emp sacce
10	Sec mitral stenosis	1/1	Pn IV	Pn IV	Pn IV	No record	Died 1/10/18	Lobar pn , L L L and Rt U , emp lt , veg endocarditis , infarcts in lt lung
11	Sec Infl	12/25-1/ 1	Pn IV	Pn IV		No record	Duty 1/3/18	
12	Sec bron	3/18-1/ 2	Pn IV	Pn IV		Resection	Prognosis (?)	
13	Primary	3/13-1/ 6	Pn IV	Pn IV		Resection	Prognosis (?)	
14	Primary		Pn II	Pn IV		Resection	Convalescent	
15	Primary	4/ 6-1/14	Pn IV	Pn IV		Aspiration	Died 1/11/18	
16	Primary	2/ 7-2/21	Strep haem	Strep haem	Neg	Resection		
17	Primary	3/12-3/13	Strep haem	Strep haem	Neg	Resection	Died 3/23/18	Bronchopn , emp sacce rt ab scesses in rt lung fibrinopur pericarditis
18	Primary	3/18-3/30	Strep haem	Strep haem	Neg	Resection	Convalescent	
19	Primary	3/ 3-1/ 1	Strep haem	Strep haem		Aspiration	Died 1/12/18	Bronchopn , emp rt sacce
20	Primary	3/13-1/ 3	Strep haem	Strep haem		Resection	Convalescent	
21	Primary	3/30-1/ 1	Strep haem	Strep haem		Aspiration	Died 1/2/18	Bronchopn emp lt L L L acute fibrino pericarditis
22	Primary	3/12-3/21	Strep haem	Strep haem		Resection	Convalescent	
23	Sec bron	3/25-3/31	Strep haem	Strep haem		Resection	Prognosis (?)	
24	Primary	1/ 5-4/ 9	Strep haem	Strep haem		Aspiration	Died 1/10/18	Bronchopn lt emp lt f fibrinous pericarditis
25	Primary	3/29-1/ 2	Strep haem	Strep haem	Neg	No record	Died 1/3/18	Bronchopn , (Interst) emp lt
26	Sec bron	3/ 9-3/20	Strep haem	Strep haem		Resection	Convalescent	

27	Primary	3/21-4/ 9	Strep haem	Strep haem		Resection	Convalescent	
28	See measles	3/26-4/ 3	Strep haem	Strep haem		Aspiration	Died 1/11/18	Lob pn rt lobe, emp rt sacc, emp lt
29	See bron	3/16-3/17	Strep haem	Strep haem		Resection	Died 3/18/18	
30	See bron, pharyngitis, G me isles	1/ 7-1/17	Strep haem	Strep haem		Resection	Convalescent	
31	Primary	3/ 4-3/ 5	Strep haem	Strep haem		Resection	Died 3/5/18	Lobar pn left lung, emp lt, central pn rt lung
32	See infl	3/ 5-3/ 9	Strep haem	Strep haem		Resection	Died 3/10/18	
33	See measles	3/24-4/ 7	Strep haem	Strep haem		Resection	Convalescent	
34	Primary	3/6	Strep haem	Strep haem		No record	Died 3/8/18	Lobar pn L L L, emp lt, mult abscesses of lung
35	Primary	12/25-1/ 6	Strep haem	Strep haem		Aspiration	Died 1/17/18	Bronchopn lt (interst) emp lt, fibrinopur pericarditis
36	Primary	3/ 1-3/ 3	Strep haem	Strep haem		Resection	Died 3/3/18	Lobar pn R L L abscess of lung, emp rt
37	Primary	3/11-3/15	Strep haem	Strep haem		Resection	Died 3/19/18	
38	Primary	2/18-2/20	Strep haem	Strep haem	Neg	Resection	Died 3/27/18	Lobar pn L L L, emp lt, pneumothorax lt infarcts of spleen
39	See infl	3/ 7-3/10	Strep haem	Strep haem	Strep haem	Resection	Convalescent	
40	See mumps	2/11-2/23	Strep haem	Strep haem	Neg	Resection	Convalescent	
41	See infl	1/23-2/11	Strep haem	Strep haem	Neg	Resection	Died 2/21/18	Bronchopn R L L, lobar pn, L U L, emp rt
42	See infl	3/ 5-3/ 5	Strep haem (?)	Strep haem		Resection	Died 3/11/18	
43	Primary	2/ 4-2/ 9	Strep haem (?)	Strep haem		Resection	Died 3/12/18	Bronchopn rt lung (interst) type, fibrinopur pericarditis, emp rt
44	See mumps	3/ 7 3/ 7	Strep haem (?)	Strep haem		Resection	Died 3/9/18	Lobar pn R L L, emp rt sacc, fibrinopur pericarditis
45	Primary	3/ 8-3/ 8	Strep haem (?)	Strep haem		Resection	Died 3/10/18	Bronchopn bilat, emp bilat sacc
46	See pharyn		Strep haem (?)	Strep haem			Died	Sarcoma testes and lung, bron- chopn, emp lt, acute general peritonitis
47	Primary	1/11-4/16	Strep haem	Strep haem		Aspiration		
48	See tonsil	1/ 5-4/ 6	Strep haem (?)	Strep haem			Died	Bronchopn bilat, emp lt sacc, fibrinopericarditis
49	Primary	1/17-1/20	Strep haem	Strep haem	Neg	Aspiration	Died 1/21/18	
50	Primary	1/17-4/21	Strep haem (?)	Strep haem		No record		
51						Resection	Convalescent	
52	Primary	1/ 1-1/20	Strep virid	Strep virid		Incision	Duty	
53	Primary	3/15	Strep virid	Strep virid	Strep virid	No record	Died 3/30/18	Bronchopn lt lung, lobar pn L L L, emp lt sacc, acute strep meningitis
54	Primary	1/ 8-1/ 4	Strep virid	Strep virid		No record	Died 1/14/18	Bronchopn (interst) rt L L, emp rt sacc, fibrinopur pericarditis
55	Primary	1/12-1/24	Strep virid	Strep virid	Neg	No record	Died 2/3/18	Bronchopn (interst), emp rt sacc, fibrinopur pericarditis

TABLE 1—DATA OF EMPYEMA CASES—Continued

No	Type of Pneumonia	Onset of Empyema	Type of Organism		Blood Culture	Treatment	Termination	Post Mortem Findings
			Sputum	Pleural				
56	Primary	12/15	Pn II	Strep virid		No record	Died 12/29/17	Bronchopn and lobar pn (bilat interst), emp lt, mult abscesses of lungs
57	See infl		Pn II	Strep haem		No record	Died 2/11/18	
58	See infl	1/ 3-2/14	Pn II	Strep haem		Resection	Prognosis (?)	
59	See tonsil, bronch (?)	1/21-2/17	Pn III	Strep haem		Resection	Recovering	Bronchopn and lobar pn (interst), emp sac rt, fibrinopur pericarditis, mult abscesses of rt lung
60	See infl, pharyn	1/18-1/26	Pn IV	Strep haem		Resection	Died 1/28/18	
61	Primary	12/22-1/20	Pn IV	Staph aureus	Neg	Resection	Died 2/11/18	
62	See bron	12/21-12/29	Pn IV	Strep virid		No record	Died 12/21/17	
63	Primary	1/22-2/18	Pn IV	Strep haem	Neg	Resection	Convalescent	Lobar pn lt lung and rt L, emp rt
64	Primary	3/4	Pn IV	Strep haem	Neg	Resection	Died 3/13/18	
65	See mumps	1/26-2/19	Pn IV	Strep haem		Resection	Convalescent	
66	See measles	12/6-1/27	Pn I	Sterile		Resection	Convalescent	General military TB, lobar pn lt lung, emp lt
67	See infl	3/27-3/30	Pn I	Sterile		Aspiration	Died 4/1/18	
68	See pleurisy	2/ 6-2/20	Pn II	Sterile	Neg	Resection	Died 3/15/18	
69	Primary	2/26	Pn II	Sterile	Neg	No record	Died 3/3/18	
70	See measles	12/18-1/ 3	Pn III	Sterile	Neg	Resection	Died 3/5/18	
71	Primary	1/30-2/25	Pn IV	Sterile		No record	Duty 4/7/18	
72	Primary	3/30-4/ 9	Pn IV	Sterile		No record		
73	Primary	1/ 3-1/25	Pn IV	Sterile		Resection	Died 1/21/18	
74	See bron	3/ 7-3/11	Pn IV	Sterile		Aspiration	Duty	
75	Primary	3/21-3/23	Pn IV	Sterile		Aspiration	Convalescent	
76	See bron	3/11	Strep haem	Sterile		No record	Died 4/19/18	
77	Primary	4/ 8-4/15	Strep haem	Sterile		No record	Convalescent	
78	See scarlet	3/30	Strep haem	Sterile		No record		
79	See bron	1/ 7-1/14	Strep virid	Sterile		Resection	Died 3/3/18	
80	See infl	3/12-3/17	Strep virid	Sterile	Neg	Resection	Duty 4/22/18	

by an organism which is rarely encountered in civil infections of the lung and pleura. In most of these cases the organism in question — the so-called *Streptococcus haemolyticus* — has been the causative agent, not only of the empyema, but of the pneumonia associated with it. The relation between streptococcus pneumonia and the incidence of empyema is well shown by a comparison of the different types of pneumonia which have been encountered at Camp Upton.

During the period from Oct 7, 1917, to April 20, 1918, 300 cases of pneumonia were admitted to the Base Hospital at Camp Upton. Of the 300 pneumonias, 283 had careful bacteriologic examinations of the sputum, 136, or almost half, were found to be of streptococcus origin, and 137 were caused by the pneumococcus. There were 49 cases of streptococcus empyema, showing an incidence of empyema among the streptococcus pneumonias of 36 per cent. On the other hand, there were only 15 cases of pneumococcus empyema, or an incidence of empyema among the pneumococcus cases of 11 per cent. Finally, there were 15 cases of sterile empyema about equally divided between streptococcus and pneumococcus pneumonia. Altogether, our records show for this period, 80 cases of empyema, and these 80 cases form the basis for this study.

Before proceeding to the discussion of empyema proper it might be well to refer briefly to the relation of measles to this disease. In some of the other camps a large percentage of the empyemas, especially those of streptococcus origin, have developed as a complication of post-measles pneumonia. Such has not been the case at Camp Upton. In the first place, a comparatively small number of our measles patients have developed pneumonia — thirty out of 164 cases, with a mortality list of but two. Furthermore, only four cases of empyema (Cases 28, 33, 66 and 70) have developed among these thirty pneumonias, and of these only two patients died. By referring to Table 1, however, it will be seen that a considerable number of the empyemas developed in pneumonias which followed influenza, tonsillitis and other mild infections. We are quite certain, however, that streptococcus empyema may develop from a primary streptococcus pneumonia. Two of the pneumonia cases which followed mumps (Cases 40 and 44) were complicated by empyema, both of these being streptococcus infections.

In this study special attention has been devoted to the bacteriologic examination of the cases. In most instances direct specimens of the patients' pleural exudate were collected as soon as the diagnosis was made, and taken to the laboratory at once for examination. The bacteriology of the sputum was carried out as follows. A fresh specimen of sputum was thoroughly washed with sterile saline and smears made for the gram stain. The sputum was then emulsified and 0.5 c c added to a tube of Avery's blood broth, which was incubated in the

water bath at 37 C for five hours. At the end of this time smears were made and if a pure culture was found agglutination tests were made at once in the usual manner. Under all conditions, however, subcultures were made from broth or plain agar plates and colonies were picked from these on the following day for further study. In many cases the blood broth method was controlled by injections of the sputum into the mouse and identification of the organism was determined from the peritoneal exudate or the heart's blood. In a few instances cultures of the sputum were made directly on blood agar plates. The results obtained by the various methods have been surprisingly consistent.

TABLE 2—CLASSIFICATION OF EIGHTY EMPYEMAS

	Cases	Deaths
I <i>Pneumococcus</i> in both sputum and pleural exudate		
Type I in both	3	0
Type II in both	4	2
Type IV in both	6	2
Type II in sputum, Type IV in pleural exudate	1	0
Sputum not examined, Type IV in pleural exudate	1 (?)	1
	15	5 (33%)
II <i>Streptococcus</i> in both sputum and pleural exudate		
Strept hemol in both	29	16
Sputum not examined, strept hemol in pleural exudate	7 (?)	6
Strept virid in both	4	3
	40	25 (60%)
III Mixed infections		
Pn Type II in sputum, strept vir in pleural exudate	1	1
Pn Type II in sputum, strept haem in pleural exudate	2	1
Pn Type III in sputum, strept haem in pleural exudate	1	0
Pn Type IV in sputum, strept haem in pleural exudate	4	2
Pn Type IV in sputum, strept vir in pleural exudate	1	1
Pn Type IV in sputum, staph aur in pleural exudate	1	1
	10	6 (60%)
IV Sterile empyemas		
Pn Type I sputum	2	1
Pn Type II sputum	2	2
Pn Type III sputum	1	1
Pn Type IV sputum	5	1
<i>Streptococcus haemolyticus</i>	3	1
<i>Streptococcus viridans</i>	2	1
	15	7 (50%)

CLASSIFICATION OF EMPYEMAS

By referring to Table 2 it will be seen that our eighty cases of empyema naturally fall into three groups (1) pneumococcus empyemas, (2) streptococcus empyemas, (3) sterile empyemas. These three groups will be discussed separately.

1 *Pneumococcus Empyemas*—In the present series of eighty cases there were only fifteen that showed the pneumococcus from culture of the pleural exudate. These pneumococcus empyemas differed in no essential respect from those seen in civil practice. Without exception

they developed in cases of lobar pneumonia in which the pneumococcus had been previously isolated from the sputum. This type of empyema usually comes on late in the course of the disease when the patient is convalescent. There is a sudden rise in temperature and a corresponding increase in pulse rate. The patient, however, may not be very ill. Frank signs of fluid are usually present and on exploring the chest over this area cloudy or creamy pus is withdrawn which on examination shows many pus cells and capsulated pneumococci.

Pneumococci of Types I, II and IV are all represented in this group, and in all except one case the same kind of pneumococcus was found in both sputum and pleural exudate. In this case (Case 14) pneumococcus Type II, atypical, was isolated from the sputum, and pneumococcus Type IV from the pleural fluid. Of this group of fifteen cases, five patients died, a mortality of 33 per cent. One patient (Case 10) developed a pneumococcus endocarditis and septicemia. One of the Type II cases (Case 7) on blood culture showed twenty-four colonies per cubic centimeter of blood, but the patient made an excellent recovery after rib resection and drainage. This patient showed a curious metastatic focus, a perithyroid abscess. In the fatal cases of this group the men all died early in the disease apparently from the intensity and extent of the pneumonia rather than from the concomitant empyema.

2 *Streptococcus Empyemas*—By far the largest number of our empyema cases were streptococcus infections, and it is this group that constitutes the most interesting phase of the problem. For convenience of discussion it will be well to divide this group into three subgroups.

- (a) *Streptococcus haemolyticus* empyema
- (b) *Streptococcus viridans* empyemas
- (c) Streptococcus empyemas following pneumococcus pneumonia

(a) *Streptococcus Haemolyticus Empyemas* In this group there were twenty-nine cases in which *Streptococcus haemolyticus* was recovered in pure culture from the empyema fluid and in which bacteriologic examination of the sputum showed the same organism. There were seven other cases in which the hemolytic streptococcus was recovered from the pleural exudate, but in which for some unavoidable reason the sputum was not examined. In these seven cases, however, the clinical course and physical signs strongly indicated a streptococcus pneumonia, so they probably belong to this group. These thirty-six cases constitute a fairly definite and characteristic picture. The patient who often gives a history of some recent infection of the upper respiratory tract is admitted to the hospital complain-

ing of cough, fever, and occasionally pain in the side. The onset, as a rule, is gradual, though it may be very sudden. Many cases are admitted with a diagnosis of influenza or bronchitis. The cough is usually dry in character and is often entirely absent, a feature which makes it difficult or impossible to collect a satisfactory specimen of sputum. The sputum itself is rather characteristic. It is usually of a white or yellowish color, quite viscid and mucopurulent. The rusty or hemorrhagic sputum of lobar pneumonia is rarely seen. The fever usually runs an irregular course, and considerable febrile periods succeeded by rapid oscillations, as in an active sepsis, appear at the onset. The pulse is comparatively slow in this early stage of the pneumonia, but is in proportion to the temperature. The respiratory rate is, however, proportionately high throughout. Pain in the side is a very inconstant symptom and when present is an additional cause of the inspiratory distress. Inspiratory pain is not usually long continued and few patients have required strapping or opiates because of it.

Physical Signs Before Onset of Empyema—The physical signs before the onset of empyema are often indefinite. On percussion, areas of dulness may or may not be present at first. Moist crackling râles are nearly always to be heard, at times confused with the pleuritic friction rub, but typical bronchial voice and breathing are rather unusual signs at the onset of the pneumonia. More often the voice and breath sounds are faint. Furthermore, one must say that there are few distinctive signs or symptoms at the onset of the pneumonia which serve to differentiate cases which subsequently develop empyema from those that do not.

Physical Signs After Onset of Empyema—In several instances patients have entered the hospital under the regimental diagnosis of empyema. Careful investigation of the history has, however, in all these instances shown a story of several days of indisposition and probable fever. Patients who have entered the hospital usually because of prostration and a slight febricula and before any physical signs indicative of either pneumonia or empyema appeared, have often developed under observation surprisingly early empyemas. Thus our group of streptococcus cases has shown a positive diagnosis of empyema possible in an average of 5.4 days after admission. When one takes into consideration the fact that three of these patients developed their pneumonia in the hospital as a secondary process two or three weeks after admission, the very early onset of streptococcus empyema is impressively demonstrated. Suffice it then to conclude that this empyema develops with surprising rapidity and often before a conclusive diagnosis of pneumonia, in addition to pleurisy, could be

made except by the assistance of the roentgen ray. It is therefore seen that these empyemas are imposed on, and do not merely succeed, the active stages of pneumonia. The prognostic significance of this fact must be apparent to all.

In our early experience with the disease we were surprised, in three instances, to find empyema at the postmortem where simple lobar pneumonia had been expected. In two of these cases the physical signs should certainly have given the diagnosis, and mere indolence on the part of the ward surgeon accounted for this failure. Careful analysis of the charts in these three cases, however, presented nothing of a symptomatic character which would lead any one unsophisticated in this epidemic to suspect the development of an empyema, for the picture was typically and solely that of a pneumonia. Nor was this finding limited to our early cases alone, for not seldom, even after we were keenly alive to the frequency of empyema, the needle and the roentgen ray have detected rapidly developing empyemas which were entirely unmarked by alterations in the clinical picture, and with strikingly few modifications in the physical signs.

One of the most constant and suggestive signs has been the appearance of profuse sweats, comparable in degree and in exhaustion to those of acute rheumatic fever. The entire surface of the body, more notably the head and the neck, are frequently beaded with large drops of sweat. These signs are unaccompanied by a chill, which is found to be a rather unusual symptom at any stage of these cases, and one which never appears but at the period of onset. Under onset we have mentioned the marked exhaustion which typifies these cases. This, however, is in no way characteristic of the empyema, since it may be also strikingly manifest in the simple streptococcus pneumonia. It is usually more pronounced when a purulent exudate is forming, or has formed, than when the pneumonia is uncomplicated. Where the exhaustion is very striking we have learned to be very constantly on guard and to apply the needle with even more diligence than ordinary, though not infrequently with negative results. Acceleration of the respiration is another suggestive sign, though of course in recognized pneumonia it can be considered as of only relative value, but there can be no doubt that as the pus begins to form there is a very perceptible increase in the respiratory rate, above that which may be attributed to the pneumonia alone, and with increase in rate is also to be found increased dyspnea and respiratory distress. There is nothing characteristic in the temperature and pulse curve in the early stage that suggests the onset of empyema. Of course, where it develops later in the pneumonia, when pulse rate and temperature are falling, an ascent in both appears. It rarely assumes a septic form, however.

In ordinary pleurisy and particularly in a process which so largely, as in these cases, involves the bases and diaphragmatic pleura, one is accustomed to consider abdominal rigidity a sign of considerable value, especially when, as is usually the case in this epidemic, it is monolateral at the onset. This sign has been strikingly absent in the cases which we present in this study. In but four of the cases do we recall this indication as demonstrable. It was often entirely absent even in instances in which we were able to demonstrate readily the fact that the diaphragmatic pleura was involved. Head zones of hyperesthesia is another frequent sign that one finds in cases of pleurisy of whatever origin, but which has not been present in our cases. Another negative sign which has impressed us very much has been the very general absence of or diminution in degree of the stabbing pain which is so generally complained of in the onset of pleurisy. This has not been frequent in our cases, even where the onset of pleural effusion seemed to take place synchronously with or but slightly later than the first pneumonic symptoms or signs. On the contrary, we have all been impressed with the frequency with which skin tenderness (not hyperesthesia) has been evident on even ordinarily vigorous percussion over the involved area. Not seldom this tenderness, which is a deep and not a superficial one, has largely determined us in selecting a point for needling.

Our study of the physical signs in general as regards this group of unusual cases has been disappointing and often the findings most difficult of explanation. As a result of great disparity between positive physical signs and lesions, our ward surgeon has been instructed to needle or fluoroscope even when all signs point away from the existence of pleural effusion. We both feel that we have "unlearned" far more physical signs of pleural fluid than we have perfected. All observers have been struck with the great frequency of skodaic resonance, and many times it has been most typical over areas from which the needle gave abundant fluid. Postmortem and roentgen-ray study of this sign has taught us to consider it as due in many instances to early pulmonary compression of more than the usual degree, because of the fact that the pleura in these cases was but little thickened, and the adjacent pulmonary tissue but little involved by consolidation. That this sign may be transmitted through a considerable amount of superjacent fluid has been demonstrated to us numerous times, and over areas where no transmission of abdominal tympany could be assumed. Probably for the same reason, breath sounds and vocal and tactile fremitus have been transmitted through massive exudates with great and deceptive distinctness. We have been forced to exaggerate alterations in these signs, or to totally ignore their appar-

ent significance. Doubtless the more limpid condition and less cell concentration of the fluid as compared with that of the antebellum conception of empyema has also something to do with the much modified physical signs. Beyond question the single physical sign which we have come to consider as of most value in the detection of these effusions is alteration in percussion. A high pitched note or the flattening of the customary resonance is a sufficient indication for a tap in these cases, and if the tap be a dry one a repetition is justified.

In six instances distinct and unmistakable pneumothorax has developed before the cases have been tapped, and in quite frequent instances minor degrees of this phenomenon appeared. In none of them could the usual explanatory causes be found present. There had been no possible injury to the thorax, no bacteria capable of causing gas formation were found in the fluid, and no possible cause of pulmonary laceration could be made out clinically, or in the three instances that came to necropsy. The amphoric splash and metallic tinkle of mingled fluid and air has come and gone in several typical cases also without a reasonable explanation. One hypothesis for these curious and surprisingly early manifestations is that they may be due to rupture of minute pulmonary abscesses, which thus allow the escape of air into the pleural cavity. Microscopic study lends some support to this theory.

In a discussion of the pathologic anatomy of the disease mention will be made of the frequent development of pleuropericarditis, and the very early appearance of this lesion is quite as remarkable as the appearance of the empyema itself. Usually when this process is present it becomes very early apparent from a primary pleuropericardial friction rub which is commonly so distinct as to become unmistakable. It diminishes, of course, as the effusion develops. As a natural sequence of this complication a pure pericarditis appears also with considerable frequency. Postmortem evidence shows that this first involves the parietal layer of the chamber, the visceral layer of the membrane only becoming involved later. Under our intensive method of study of the cases, the complication has only rarely escaped detection clinically. The amount of fluid which may thus accumulate in the sac may be very large — as much as 900 c c, for example. The character of this fluid is precisely like that seen in the pleural cavities. First, it has a typical clear to turbid urine appearance, later on it becomes highly fibrinous, with the characteristic deposit of fibrin on both layers of the membrane and the ultimate transformation into pus of a clinical type. The bacteriology of the pericardial exudate coincides with that of the pleural fluid.

There are no signs or symptoms that appear in the pericardial complication which differ from those customarily seen in this condition. In two instances the pericardial sac was drained, once early in the course of the complication, once late after the fluid had become a thick and gelatinous pus. Both patients recovered.

Study of the total and differential white cell count has been very disappointing as a diagnostic measure. With the acknowledged existence of the pneumonia there is nothing shown suggestive of a developing exudate, nor of the fact that this fluid is of a highly septic character.

The blood pressure is that usually seen in pneumonias. Of course in fatal cases the pulse pressure becomes very much diminished as death approaches, and with it the usual tachycardia and cardiac arrhythmias which are common to the immediate premortem status.

The urine provides no data of an unusual character and nothing of a diagnostic value.

The roentgen ray has been used in almost all cases, in diagnosis, not so frequently for the demonstration of fluid as to indicate the extent and nature of the pulmonary process. In most cases so far as the demonstration of empyema is concerned the roentgen ray, particularly stereoscopic plates, have been most useful. It is much more necessary for the location of pulmonary disease. In several instances it has been misleading, indicating no fluid where the needle showed it to be present and less frequently the opposite fault has been found. The fluoroscope has not always been employed as a diagnostic routine for the reason that most of our patients have been so gravely ill that they could not be set up. It was soon found that satisfactory plates could only be obtained when the patient was raised up on a rack and kept in this position for a short period until gravity had caused the fluid to occupy a dependant part of the thorax. For a most satisfactory method of accomplishing this we are much indebted to our colleagues at Camp Devens, who first demonstrated their excellent practice to us. Our experience has shown us, however, that one may not depend absolutely on the roentgen ray in the diagnosis of empyema. In other instances it has misled us where the fluid was encapsulated at the left internal and posterior angle of the thorax, and its shadow obscured by that of the heart. The use of the roentgen ray is indispensable in the diagnosis of empyema, but it will not alone keep the lazy clinician out of trouble with the pathologist.

Frequent needlings have been most certain and more satisfactory in our hands. Where the puncture was to be made for diagnosis only, a fine hypodermic needle from 3 to 4 cm. in length attached to an ordinary 5 c.c. Luer syringe is used. The fluid in most questionable

instances is so limp that it can be very readily obtained in this manner in sufficient quantity for bacterial and histologic diagnosis, and the pain caused by this needling is so slight that the patients do not object to frequent taps. We ordinarily do our aspirations with the Potain aspirator, but sometimes when the amount to be aspirated is small, an ordinary 20 c.c. glass syringe is used. We cannot commend the use of the needle too highly. It is indispensable in diagnosis.

Character of the empyema fluid. The pleural exudate when removed is usually light yellow, often with a greenish tinge, and in the early stages only slightly cloudy. Later in the disease it may take on a distinctly purulent character. Smears from the fluid show pus cells in large numbers, and large round or slightly flattened cocci arranged in short chains of from two to ten organisms. We have observed that the bacteria are much more numerous in the streptococcic empyema than in the pneumococcic empyemas. Cultures from the exudate on blood agar plates show, after twenty-four hours' incubation, many small, elevated, opaque, colonies of a pearl-gray color, each surrounded by a sharply defined zone of hemolysis. Subcultures in blood broth produce diffuse clouding of the medium, with a heavy sediment in the bottom of the tube. Rapid destruction of the blood cells takes place and the blood broth takes on a brilliant, claret-red color. Smears from the blood broth show chains of cocci similar in all respects to those seen in the smears from the pleural exudate.

The mortality rate in this group was very high, our experience in this respect corresponding to that met by clinicians in other camps. Of the thirty-six cases, twenty-two patients died, a mortality rate of 61 per cent.

(b) *Streptococcus Viridans Empyemas*—In this group of cases cultures from both the sputum and the pleural exudate showed a streptococcus of the nonhemolyzing variety. There were found four cases of this type (Nos. 52-55). Clinically, these cases have differed in no respect from the *Streptococcus hemolyticus* cases. All four of these were cases of bronchial pneumonia, and the symptoms and signs of empyema were similar in every way to those of *Streptococcus hemolyticus* empyema. Three out of the four patients died.

(c) *Streptococcus Empyemas Following Pneumococcus Pneumonias*—This very interesting group of mixed infections consists of nine cases (Nos. 56-65) and corroborates the findings of Cole and McCallum at Fort Sam Houston. In these cases the pneumococcus was cultivated from the sputum, but cultures from the pleural exudate gave streptococcus, either hemolyticus or viridans. Pneumococci of Type II, III and IV are represented in this group of mixed infections. There is also a case (Case 61) which we include in this group which

gave pneumococcus, Type IV, in the sputum, but *Staphylococcus aureus* in the exudate. It is possible, however, that in this case the staphylococcus infection developed after operation and drainage had been performed. The majority of these cases were frank lobar pneumonias. There were two cases diagnosed bronchopneumonia, and it may have been that in these two cases mouth pneumococci confused the bacteriologic picture. This was also a highly fatal group, six out of ten patients dying. Clinically, the empyema in this group possessed all the characteristics of the pure streptococcus type.

Summarizing these three subgroups, there were forty-nine streptococcus empyemas with thirty deaths, a mortality rate of 61 per cent.

3 *Sterile Empyemas*—In addition to the sixty-five empyemas already mentioned, we have included in our study fifteen cases (Nos 66-80) in which fluid of a purulent or semipurulent nature was removed from the pleural cavity, but from which cultures were sterile. In several of these cases gram-positive cocci were seen in smears from the fluid. They usually showed, however, some sign of disintegration and could not be cultivated even on blood medium. Ten of these empyemas were associated with pneumococcus pneumonias of the lobar type, and five patients died. Five cases were associated with streptococcus pneumonia and two of these patients died.

Blood Cultures—Blood cultures were made on twenty of our empyema cases, with only three positive results (Nos 7, 10 and 39). Two of these were pneumococcus cases and one *Streptococcus haemolyticus*. In the early part of the year, blood cultures were taken on every case of pneumonia, but when it was found that the results were almost universally negative this procedure was discontinued as a part of the routine examination. The clinical picture might lead one to suspect that this disease was one phase of a general septicemia. The character of the temperature curve, the pulse rate, the profound prostration, the rapid course of the disease and the high mortality all support this impression. The rare occurrence, however, of metastatic foci points strongly against this theory. Strangely enough, two out of the three patients in whom the blood culture was positive made uneventful recoveries.

PATHOGENESIS OF EMPYEMA

All of our cases of empyema have been associated with pneumonia, but in many of the streptococcus cases the pneumonic process has been relatively slight, as verified by physical signs, the roentgen ray and necropsies. Cases of *Streptococcus haemolyticus* empyema have been reported from other camps in which no evidence of con-

comitant pneumonia could be obtained, and such a phenomena seems possible in consideration of our own experience. It is quite certain that in many cases the empyema has far outweighed the pneumonia in clinical importance. It is probable, however, that in the majority of cases streptococcus empyema develops from a bronchopneumonia, the infectious organism being conveyed to the pleura either by the way of the lymphatics or by the direct extension of one of the small abscesses so frequently seen, through the pleural coat. The severity of the pneumonia may be a factor in the development of the empyema, but this is a difficult point to settle, since the onset of the empyema early in the course of the disease masks the real character of the pulmonary condition. It may be stated, however, that streptococcus empyema has usually appeared in those cases of pneumonia that have seemed to be severe infections.

The question if ward infections occur in this disease, that is, patients suffering from pneumonia of whatever type are likely to contract a streptococcus empyema from their associates in the ward or from streptococcus carriers, receives some confirmatory evidence from the fact that our group of cases includes nine instances in which a pneumococcus infection of the lung was followed by a streptococcus empyema. On the other hand, we have seen nothing clinically that would seem to substantiate this hypothesis, and since we have adopted careful methods of isolation of cases in the wards by means of screens and punctilious gowning, capping and veiling of attendants, nurses, physicians and convalescent patients, no change in the incidence of empyema has been evident. It is interesting to note that our camp was entirely free from streptococcus empyema until we received a large contingent of colored troops from another encampment said to have suffered much from this condition. This complication is no longer limited to "ultrabrunettes" with us at Camp Upton.

The likelihood of an autogenous infection from streptococci already in the mucous tract of patients before they contract the pneumonia seems to us a much more probable factor. This has received suggestive corroboration at Camp Upton from a series of cultures made during an epidemic of streptococcus pharyngitis in the convalescence of which a considerable number of streptococcus pneumonias developed.

PATHOLOGY

Altogether, twenty-seven of the empyema cases came to necropsy. Three of these (Cases 6, 9 and 10) were pneumococcus empyemas, one gave sterile cultures and the remaining twenty-three all showed streptococci in smears and cultures.

The three pneumococcus cases were associated with typical lobar pneumonia, with consolidation in the side involved. The fluid in all three of these cases was frankly purulent, and in one case there were pockets of pus between the lobes of the lung. One case was associated with acute vegetative endocarditis of pneumococcus origin. In all three cases the pleura was covered with a thick layer of fibrin, which could be readily removed from the underlying membrane.

The one post mortem case (Case 70) of empyema from which cultures during life had been sterile showed at necropsy pulmonary tuberculosis and tuberculous pleuritis.

The remaining group of twenty-three cases all showed streptococci in pleural exudate. Three of these cases (Cases 56, 62 and 64) belonged to the mixed group of infections. They had been classified from sputum examination as pneumococcus infection of the lungs. The cultures from the pleural exudate gave in two cases a non-hemolyzing type of streptococcus, and one case the hemolytic streptococcus. At necropsy all showed typical lobar pneumonia, but in addition, patches of bronchopneumonia were present in those portions not involved in the lobar process. In three other cases (Cases 53, 54 and 55) bacteriologic examination of both sputum and pleural exudate gave the nonhemolyzing or green streptococcus. All three of these cases showed a patchy type of consolidation and were classed as bronchopneumonias. The empyema in this group was of the sacculated type and the fluid was cloudy, yellow and full of flecks of fibrin. In two cases (Cases 54 and 55) which showed purulent pericarditis, the process was apparently an extension by direct contiguity from pleura to pericardium, for the pleura adjacent to the pericardium was extensively involved.

The third subgroup in this division is that in which the process in the lungs and the pleura was all of *Streptococcus haemolyticus* origin. There were seventeen of these cases that came to necropsy. Eleven were diagnosed as bronchopneumonia and six as lobar pneumonia. The empyema in this group was described as sacculated in half the cases, in the other cases the fluid was lying free in the pleural cavity. The fluid was sometimes cloudy and amber-colored and sometimes distinctly purulent. In the former group there were often a number of large, entirely separate pockets which did not communicate with one another. One such pocket was frequently found between the pericardial sac and the anterior flap of the left lung which lies over it. This probably accounted for the frequency of pericarditis in this group.

The lung on the affected side in these cases is covered with a fibrinous coat which varies in thickness with the age of the empyema. It is closely adherent to the pleura. The lungs in these streptococcus cases

have nearly all shown the changes described by Cole and McCallum as interstitial bronchial pneumonia. The lung is atelectatic, due to the compression caused by the fluid. On section the bronchioles stand out with remarkable distinctness and are usually filled with pus. The walls of the bronchioles appear thicker than normal and there is an over-growth of fibrous tissue throughout the organ which accentuates the fibrous trabeculae. The thickening about the bronchioles may be so marked as to give them the appearance of small tubercles or miliary abscesses. Even in those cases in which a part or all of a lobe is consolidated, these changes have been observed in other parts of the lungs.

Microscopic sections of the lungs in these cases show areas of bronchopneumonia around the bronchioles and an extensive infiltration of small round cells about the bronchioles and blood vessels. There is a marked tendency toward organization of the exudate in the alveoli, which consists of unusually dense fibrin, lymphocytes and desquamated epithelium.

The pleural covering has been converted into a thick coat of granulation tissue, on the surface of which there is a layer of fibrin and leukocytes. Small miliary abscesses have been observed in cases, sometimes occupying the site of a bronchiole and at other times situated so as to displace a number of the alveoli. In one case these minute abscesses were located about the small blood vessels.

OTHER PATHOLOGIC CONDITIONS ASSOCIATED WITH EMPYEMA

The only other pathologic condition which occurred with any frequency was suppurative pericarditis. This was found altogether in nine cases, eight of which were in the streptococcus series and one in the cases of mixed infections. In one other case a fibrinous pericarditis was found, and in this latter case it was easy to understand why the pericarditis accompanies the empyema so frequently. That portion of the parietal pericardium which lay in immediate contact with the left pleura was intensely reddened and covered with a fresh deposit of fibrin. The infection had apparently extended into the pericardium by direct contiguity, probably by way of the lymphatics. In quite a number of these infections of the pericardium a pocket of pus was found between the pericardial sac and the adjacent portion of the left lung.

Abscess of the lung was the next most common pathologic finding and was noted in five cases. These abscesses were usually small and multiple, but in one case there was a single large abscess located in the center of the consolidated area.

Infarcts were found in two cases (10 and 38), once in a pneumococcus empyema and once in a *Streptococcus hemolyticus* case

Acute vegetative endocarditis was noted in one of the pneumococcus cases (Case 10), while acute general peritonitis (Case 46) and acute suppurative meningitis (Case 53) were each observed once, and each in connection with a streptococcus infection

Bilateral empyema was noted in only two cases, once in a pneumococcus case and once in a streptococcus case

It will be seen from this summary that in spite of the virulence of this infection it was usually confined to the lungs and pleura, with occasional involvement of the pericardium. This would seem to indicate, as already noted, that the disease is not essentially a septicemia

TREATMENT

It has not been our original intention to attempt to consider this phase of the subject extensively in this paper. Perhaps our mortality rate in the streptococcus pneumonias should suffice as an excuse for this reticence on our part, but we do feel it necessary at least to outline what in our experience should not be done in the hope that it may be of assistance to others who are dealing with these same problems. At the outset we feel ourselves forced to say that the unfortunate interference of lay military commanders in the matter of necropsies must be held responsible to some extent for failures in treatment and the much longer and costlier method of forcing us to solve this problem by experiment rather than from the more exact knowledge which the postmortem alone gives to serious inquiring clinicians

It is of course obvious that since most cases of streptococcus empyema develop very early in the course of pneumonia, it cannot do in case operative measures are decided on to use general anesthetics, nor does it seem wise to trust the after-treatment of such cases to surgeons alone. Entire cooperation must exist between the medical and surgical departments, and these patients, even though operated on, should be still considered as properly under medical charge

In ordinary empyema of pneumococcus type we think there can be but little question that in the larger number of cases diagnosis should be followed by early operation. This older idea has been confirmed in our minds by such cases of this class as have occurred in this epidemic. As in the usual run of cases, operation has in most instances been followed by prompt benefit and reasonably early recovery. The results have been decidedly different in our cases of streptococcus empyema, as also in those so-called sterile empyemas which we believe are likewise of streptococcic origin

In eleven of our twenty-two fatal cases in the *Streptococcus haemolyticus* group the men have been operated on, most of them in the relatively early stages of the empyema, and of the fifteen men who have recovered or are still in the hospital, but eight had a resection done. Study of this recovery list, however, has apparently shown that those patients operated on early have, almost without exception, died, while those in whom the operation has been postponed until the pus became thick and gelatinous (frequent aspirations in the meantime having been made), recovered.

As a result of our study of this group we have naturally arrived at the practice of withholding our cases from the surgeon until later in the course of the disease, when the pus has become thick with fibrin and cells.

We have felt that our better success since this method had been adopted has depended in part on the fact that when the pleural cavities are drained through the active stage of the pneumonia the rapid collapse of the diseased lung on the operated side has thrown an added strain on the unprepared heart, which has been a dominant factor in the cause of post operative death. Furthermore, when the waiting policy is pursued, not only may the pneumonia improve and the heart adjust itself to the strain thrown on it, but it has been our observation that the pleura becomes so thickened as a result of the exudate that the subsequent collapse of the lung following thoracotomy is less marked.

We may summarize our present procedure briefly as follows, but while our results are now better than formerly, we at the same time acknowledge that they are very far from satisfactory.

The case is carried as an ordinary case of pneumonia. As soon as the fluid is discovered (and with the persistent use of the needle and roentgen ray this is usually very early determined) the aspirated diagnostic specimen is examined by smear and culture. If the exudate is clear, notwithstanding the presence of streptococci, it is allowed to remain in the chest until it is apparent that the fluid is embarrassing respiration, in which case it is aspirated by the Potain aspirator. This aspiration is repeated as frequently as seems indicated, and careful watch is maintained on alterations in the character of the fluid. When it becomes thick and viscid, the case is deemed to have reached the stage for surgical intervention.

Meantime, of course, the general symptomatic treatment of pneumonia has been followed. As a rule, digitalis is given freely in the early stages and camphor, epinephrin, caffeine, etc., are given as symptomatically indicated. The usual attention is given to elimination, to abundant aeration, and in suitable cases the patients are placed out of doors exposed to the sun and air. Temperature is controlled in part,

at least, by hydrotherapy and aerotherapy, and where much pain is suffered or when the patient coughs incessantly or becomes excitable, codein or morphin is used as indicated

We are most anxious to attempt treatment of these cases by the use of an antistreptococcus serum, and steps in this direction are now being taken We feel that until some protective mechanism is discovered we shall continue to find these cases most unfortunate problems in military medicine

A marked improvement in results has followed the surgical treatment of these cases of hemolytic streptococcus empyema since they have been placed exclusively under the care of a single surgeon (Captain Perry), who has made a special study of this condition, and particularly of its surgical management

SUMMARY

A highly virulent type of empyema has been prevalent at Camp Upton during the winter and spring months of 1918

Eighty cases have been observed in a series of 300 pneumonias

Fifteen of these were caused by the pneumococcus, fifteen others were sterile, the remainder of the cases were caused by a streptococcus, usually of the hemolytic type

In this series of cases empyema has been constantly associated with pneumonia of either the bronchial or lobar type Usually a bronchopneumonia has accompanied a streptococcus empyema, and a lobar pneumonia the pneumococcus empyemas

In the great majority of cases the organism which has been found to be the causative agent in the pneumonia has also been isolated in pure culture from the pleural exudate In nine cases, however, a pneumococcus pneumonia was associated with a streptococcus empyema

The onset of the pneumonia and the empyema is apparently simultaneous in some cases

This epidemic of empyema has been, in large part, independent of measles and other similar infections

The clinical symptoms and the physical signs differ from those of classic empyema

Diagnosis is frequently difficult by reason of the equivocal physical signs and the indefinite symptomatic picture Diagnostic aspirations are the most certain means of discovery of the condition in its early stage The roentgen ray stands second in diagnostic importance Of the physical signs, alterations in percussion seem to be the most helpful

The interstitial type of bronchopneumonia, recently described by Cole and MacCallum, is usually found associated with streptococcus empyema

Fibrinopurulent pericarditis is the most frequent complication
Pyopneumothorax has also been observed in a number of cases

The mortality rate is high and the prognosis is serious

Medical treatment is essentially expectant

The most efficacious method of surgical treatment and the correct time for its application are yet to be determined

VOLUNTARY ACCELERATION OF THE HEART BEAT*

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Favill and White¹ have recently studied a person having the ability to increase the rate of the heart at will. This was the fourteenth of such persons to be reported (see Footnote 2). Electrocardiograms have been made of three of these persons, but only in the studies of Favill and White were the effects of atropin on the ability to accelerate observed. These authors, with others who have studied similar instances, were led to believe that the action of the accelerator nerves was the chief factor in the mechanism of this type of acceleration.

The following observations are reported in order to add another case to the series and because certain differences in results were obtained from those previously recorded.

The subject is a young medical student who is entirely healthy and is apparently free from all physical and neurotic defects. He has had no cardiovascular symptoms whatever and physical examination shows the heart to be of normal size and free from abnormal sounds and murmurs. Attacks of tachycardia have never been noticed. He discovered the ability to increase his heart rate voluntarily during the course in physiology in his freshman year and has practiced it only at times of making observations such as the following.

Electrocardiograms were made with an instrument of the Cambridge pattern so standardized that a deflection of 10 mm was produced by a current of 1 m. volt. Continuous rolls of bromid paper were used so that the records covered fairly long periods of time. Radial pulse tracings were made with a Mackenzie polygraph, and blood pressure readings were made before and during periods of acceleration. The effects of large doses of atropin were tested.

During the period of acceleration there is a very slight increase in

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* From the Medical Clinic of the Peter Bent Brigham Hospital and the Harvard Medical School.

1 Favill, J., and White, P. D. *Heart*, 1917, **6**, 175.

2 Koehler, M. *Arch f d ges Physiol*, 1914, **158**, 579. Pease, E. A. *Boston Med and Surg Jour*, 1889, **120**, 525. Tarchanoff, J. R. *Arch f d ges Physiol*, 1885, **35**, 109. Tuke, D. H. *Illustrations of the Influence of the Mind on the Body in Health and Disease, Designed to Elucidate the Action of the Imagination*, London, 1872. Van de Velde, Th. H. *Arch f d ges Physiol*, 1897, **66**, 232.

the rate and the depth of respiration (Fig 3), and the pupils dilate moderately as recorded by other observers No definite physical effort is made, but constant mental concentration must be maintained, which, after several closely repeated trials, becomes quite fatiguing

Figure 1 shows a radial tracing and illustrates a typical period of acceleration of short duration The rate begins to increase almost immediately following the word of command and reaches its maximum after about ten heart cycles All our tracings show a decrease in amplitude of the pulse waves rather than an increase with marked dicrotism, as shown by Favill and White ¹

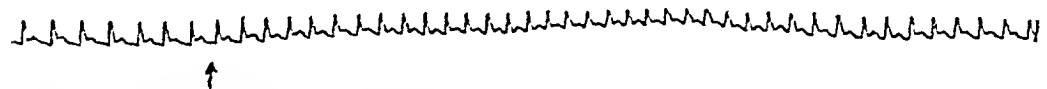


Fig 1—Radial tracing showing typical period of acceleration of short duration Command to accelerate indicated by arrow

There was a distinct rise in blood pressure with each acceleration with the exception of the effort at the height of the atropin effect, when there was a drop of 10 mm from the reading made five minutes before The latter reading, however, was 10 mm higher than the first record made before the atropin was given The greatest increase noted was one of 18 mm accompanying an acceleration of 27 beats per minute (See accompanying table)

TABLE GIVING DATA OF AUTHOR'S CASE

Time, P M	Pulse Rate	Increase	Blood Pressure		Remarks
			Systolic	Diastolic	
4 20	69	.	120	70	Voluntary acceleration
4 22	96	27	123	75	
4 25	66	.	120	70	
4 27					Atropin 0.002 gm subcutaneously
4 30	60				Beginning dryness of mouth Pupils slightly dilated, mouth very dry
4 55	66		120	70	
5 10	74		115	70	
5 15	86	12	130	75	Voluntary acceleration
5 20	94		130	70	Dizzy, slightly nauseated
5 25	102	8	120	70	Voluntary acceleration
5 35					Cardiogram taken (Fig 4)
5 45	76		134	80	Dryness slightly less marked

Electrocardiograms of this student show no distinctive characteristics other than a slight notching of R and a diphasic T in the third lead. There is a definite, but not unusually marked, sinus arrhythmia (Fig 2). During the periods of acceleration (Fig 3) there was no change in the P-wave, in the P-R interval, nor in the distance from the beginning of R to the end of T. The amplitude of T was not changed. There was some rhythmic variation in the height of R both

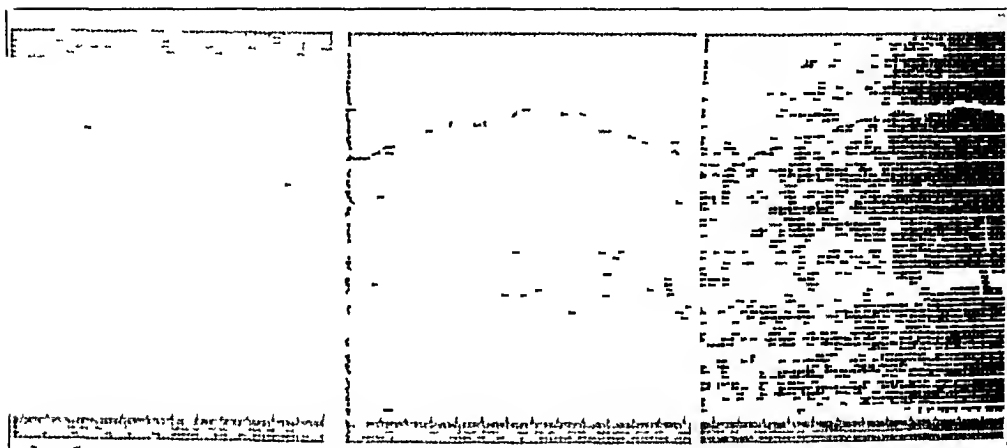


Fig 2—Leads I, II and III of subject at rest. Time in $\frac{1}{6}$ and $\frac{1}{25}$ second

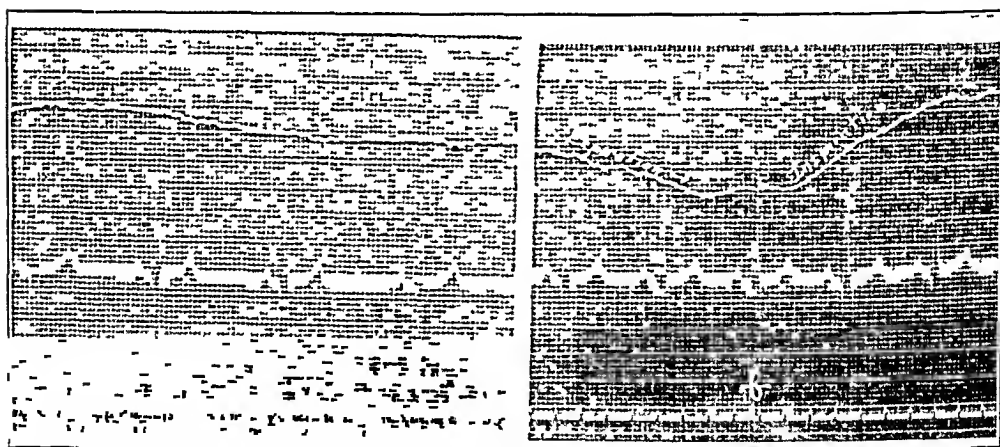


Fig 3—Lead II, *a*, just before command to accelerate, *b*, at height of acceleration. Line above electrocardiogram records respiratory movements obtained by pneumograph and tambour

before and during the period of acceleration. The general average of the R deflections was slightly lower during the periods of acceleration, but by not more than one-tenth of the height preceding the increased rate.

After subcutaneous injection of 0.002 gm of atropin sulphate the rate was increased from 69 to 94 beats per minute. Electrocardiograms taken at this time show a very slight increase in the amplitude

of T in the first lead and a correspondingly slight decrease in the height of R. No change in the distance from the beginning of R to the end of T could be made out. The sinus arrhythmia was almost, but not completely, obliterated. If one calculates minute rate on the shortest and longest cycles shown by the electrocardiogram at this time, a difference of 8 beats per minute results, which corresponds to the acceleration noted at the wrist as shown in the table. The ten beats preceding voluntary acceleration at the height of the atropin effect occurred at the rate of 80 per minute, the ten beats at the height of voluntary acceleration at 87 per minute, an increase of seven beats.

When respirations were forced without atropin the sinus arrhythmia becomes more marked as shown in Figure 5. If the rate were calculated on the basis of that seen at the beginning of inspiration,

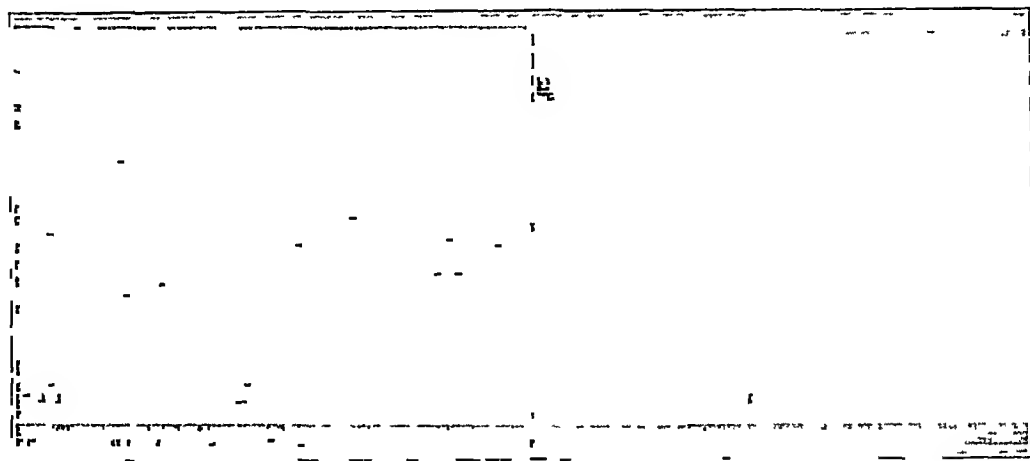


Fig 4—Lead II, sixty-eight minutes following injection of atropin *a*, just before command to accelerate, *b*, at height of acceleration

where it is most rapid, it would approximate 79 per minute. If calculated on the expiratory rate it would give approximately 54 beats per minute, or a difference of 25 beats. The greatest voluntary acceleration recorded in our observations was one of 27 beats per minute, which it would seem could be easily accounted for by vagus activity, assuming that sinus arrhythmia of the respiratory type is due to rhythmic changes in vagus inhibition. Pressure on the right vagus produced a prompt slowing of the heart rate from 72 to 48 beats per minute.

DISCUSSION

The identification of the mechanism involved in these cases is somewhat difficult and perhaps cannot be definitely attributed to either vagus or accelerator action alone, for there are probably no stages in the heart's activities in which both are not active to a greater or less extent. It would seem, however, that in this person our observations

point more to vagus than to accelerator domination during periods of acceleration. We have not been able to observe the marked decrease in the amplitude of R nor the increase in P and T during the increased rate as recorded by Favill and White and mentioned by Lewis and Cotton³—quoting Rothberger and Winterberg—as characteristic of effects of stimulation of the stellate ganglia. Nor have we obtained any decrease in the length of systole which was so marked in the experiments of Hunt⁴ following direct stimulation of the accelerator nerves and by Patterson⁵ following intravenous injection of epinephrin.

Animal experiments have also shown that following stimulation of the accelerator nerves there is a prolonged latent period, from five to ten seconds while the acceleration in these persons showing volun-

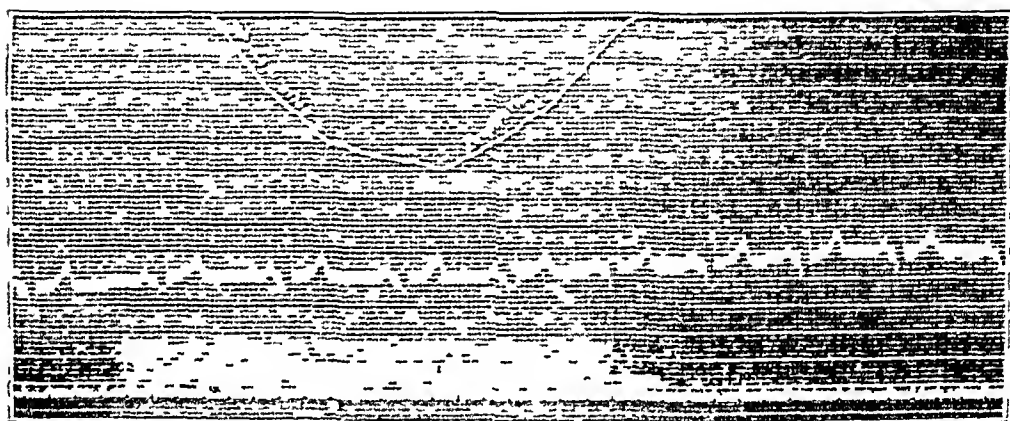


Fig 5—Electrocardiogram taken during period of forced respiration

tary control begins almost immediately, reaching a maximum, it is true, after a few seconds of effort.

Then again, the degree of acceleration during our observations seemed to be definitely within the extremes of rate shown in a study of the normal sinus arrhythmia. The results following injection of atropin were quite at variance with those reported by Favill and White, who found no reduction in the ability to accelerate. As has already been pointed out, there was a definite and corresponding decrease in the sinus arrhythmia and the ability to accelerate at the height of the atropin effect in our observations. Had the atropin been given in sufficiently large dose completely to paralyze the vagus terminals we believe the ability voluntarily to change the rate would have been abolished or nearly so.

3 Lewis, Thos., and Cotton, T. F. *Proc Physiol Soc.*, June 28, 1913

4 Hunt, R. *Am Jour Physiol*, 1899, **11**, 395

5 Patterson, S. W. *Proc. Royal Soc.*, 1915, **88**, 371

Gasser and Meek,⁶ after studying the mechanism of acceleration accompanying exercise, were led to conclude that the primary increase was due to a decrease in vagus inhibition, but that this was probably augmented "in times of great need" by accelerator influences. Our observations are entirely in accord with this view. It may be that those persons showing higher degrees of voluntary increase in rate may be able to add accelerator stimuli to a primary vagus release.

6 Gasser, H. S., and Meek, W. J. *Am Jour Physiol*, 1914, **34**, 48

ACUTE ENDOCARDITIS FOLLOWING WAR WOUNDS

INCLUDING NOTES OF HEART WEIGHT AND ARTERIOSCLEROSIS IN SOLDIERS ~

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In a previous report¹ observations on the necropsies on eighty-seven soldiers who died in active service in France were recorded, reserving for separate study certain features of the pathology of the cardiovascular system. This seemed justifiable because of the relatively large number of cases of acute endocarditis observed. It is no new fact that acute endocarditis may accompany septicemia and pyemia, but surgeons and internists often regard the soldier as resistant to such complications and neglect this possibility in their treatment of the case. The experience of the writer in France has led to the belief that treatment can be successfully modified by a consideration of the changes in myocardium and renal parenchyma which may permanently handicap the soldier in after life. This study was taken up in the hope that light might be thrown on a subject by no means new, but as yet far from being satisfactorily explained.

As a corollary to the studies of acute endocarditis a study of the weight of the heart is presented and also a note on the occurrence of arteriosclerosis.

Acute endocarditis was observed in fourteen of the eighty-seven necropsies. There is no assurance that a similar percentage would be seen in a larger series of cases, but data should be collected. The number is large enough to be suggestive and to direct the attention of pathologists and clinicians toward minute observation of the valves in life and after death particularly in cases of septicemia or pyemia.

TYPE OF CASES

Of the fourteen cases showing acute valvular lesions, twelve were pure acute disease and two showed acute lesions superimposed on preceding chronic lesions. The twelve acute cases showed involvement of the aortic valve alone in five cases, the mitral, two cases, the pulmonary, one case, the tricuspid, one case, combined mitral and aortic, three cases. One case showed chronic mitral stenosis with

* Submitted for publication June 12, 1918

1 Necropsy Service in a Military Hospital in the Field, appearing in *Am Jour Med Sc*, June, 1918

acute mitral and aortic lesions, one case showed chronic mitral and aortic stenosis with acute mitral lesions. The *Staphylococcus pyogenes aureus* was isolated in three cases, two of which were pyemias and one was a septicemia. The *Streptococcus pyogenes* was isolated in nine cases, two of which were pyemias and seven were septicemias. Two cases were clinically and pathologically septicemias, but were not demonstrated to be so bacteriologically. All had suffered serious primary wounds, five of which involved joints and four others of which involved other serous cavities. These wounds are irregularly distributed in regard to the valves attacked except that both the cases showing superimposition of acute on chronic lesions were penetrating wounds of the pelvis. In contrast to these figures, there were six cases of infected wounds of the joints which failed to show endocarditis, twenty-three cases of wounds of other serous cavities not including head wounds and forty-two cases of septicemia or pyemia without noticeable lesions of the endocardium.

AVERAGE DURATION OF ILLNESS

As to the duration of illness, one patient, a case of gas gangrene, succumbed in four days. The other thirteen patients were all ill one week or more, eight were ill more than two weeks, five more than three weeks, four more than four weeks, and one was ill more than five weeks. The average duration of illness was eighteen days as compared with an average of seventeen days in forty-two septic cases without endocarditis.

TYPE OF ORGANISM FOUND

All the cases were obviously either septicemia or pyemias and the *Streptococcus pyogenes* was the predominant organism. One case showed perfringens in the blood after death, but all the work with this organism tends to show that it is not an invader of the blood stream during life. The case in question appeared to be septicemic as the result of pyogenic infection before the gas gangrene developed. It is not believed that *Bacillus perfringens* caused the acute endocarditis of this case.

AGE AND TERM OF SERVICE

The fourteen cases, as a group, averaged $29\frac{1}{2}$ years of age and twenty-four and one-half months' service, somewhat greater in each instance than the averages for the entire group studied (27 years of age, twenty-two months' service). It may well be that the greater age and prolonged service might have reduced the resistance of these persons so as to expose them to this serious complication.

This information is summarized in Table 1.

TABLE 1—SUMMARY OF THE STUDY OF CASES OF ACUTE
ENDOCARDITIS IN FOURTH SOLDIERS

Lesion	Case No	Age in Yrs	Service in Mos	Illness in Days	Wound	Disease	Organism
Acute aortic valvulitis	10	43	33	31	Buttock	Pyemia	Streptococcus
	12	22	19	50	Hip joint	Septicemia	Streptococcus
	25	34	25	16	Thigh	Septicemia	?
	30	28	36	22	Chest	Pyemia	Streptococcus
	51	35	15	17	Shoulder	Septicemia	Streptococcus
Acute mitral valvulitis	7	23	22	7	Knee joint	Septicemia	Streptococcus
	76	20	16	10	Chest	Septicemia	Streptococcus
Acute pulmonic valvulitis	2	22	24	29	Ankle joint	Septicemia	Streptococcus
Acute tricuspid valvulitis	9	29	12	28	Foot	Pyemia	Staphylococcus
Acute mitral and aortic valvulitis	14	29	36	7	Thigh	Septicemia	Streptococcus
	21	21	16	18	Knee and elbow joints	Septicemia	Streptococcus
	40	36	18	4	Leg	Gas gangrene	Perfringens
Acute superimposed on chronic valvulitis	20	34	35	14	Pelvis	Pyemia	Staphylococcus
	75	37	36	8	Pelvis	Pyemia	Staphylococcus

NOTE—Streptococcus signifies a gram positive organism in long chains. Staphylococcus signifies Staphylococcus pyogenes aureus. Pyemia indicates abscess formation in more than one organ.

TYPE OF LESION

The aortic lesions were in all cases extremely mild and might easily have been overlooked on less careful examination. It is of further interest that in all the aortic cases in which an organism was identified (six of the seven cases) the *Streptococcus pyogenes* was found, and this is true also of the acute mitral lesions. Both cases of acute valvulitis superimposed on chronic lesions were in association with *Staphylococcus pyogenes aureus*. The pure aortic cases show a rather high age incidence as compared with the other cases excepting the two patients who had acute and chronic lesions. This same group of men appeared to have been in active service somewhat longer than the other cases. From the mildness of the aortic disease and the apparently long duration of illness in these cases it might be assumed that this valve is somewhat more resistant to acute disease than are the other valves, but this view is more than counterbalanced by the large number of cases in which aortic disease appeared. It can be stated, however, that whereas acute aortic disease is common it does not become as severe and extensive as disease of the other valves, a fact in accordance with observations in civil life.

Of considerable interest is the occurrence in the fourteen cases of two cases with valvular disease of the right side of the heart only. This is extremely uncommon in adult life, but an examination of the data in these cases shows no explanation for their occurrence.

In only one case did the acute valvulitis appear to be of undoubted embolic origin, namely, the case of acute tricuspid disease, the lesion appearing as an ulcer in the middle of the valve flap and associated with what appeared to be an abscess in the substance of the valve. The case of pulmonic disease might have had a similar origin, for at the necropsy the lesions covered the ventricular surfaces of the leaflets and might have originated as emboli in the substance of the leaflets. All the other cases appeared to originate at the line of closure. According to the work of Bayne-Jones,² normal vascularization of the leaflets extends to the line of closure in the auriculo-ventricular leaflets, but only a short distance into the semilunar leaflets. Hence, lesions of the line of closure of the semilunar leaflets probably are not of embolic origin, whereas those of the line of closure of the mitral and tricuspid leaflets may or may not be.

CHRONIC VALVULAR LESIONS

There were four cases of chronic valvular disease without acute lesions, two of which were septicemias of rather short duration (five and ten days). The two cases of meningitis lived longer but were probably not septicemic. Of the two septicemic cases, one showed a sclerosis of the valve rather than a true chronic inflammatory process, leaving one case of chronic valvulitis with septicemia and without acute lesions as contrasted with two other cases with chronic valvulitis, pyemia and a superimposed acute lesion. This is in accord with the old view that a true chronic valvulitis predisposes to subsequent acute attacks (refer to Table 2 for summary).

TABLE 2—CASES OF CHRONIC VALVULAR DISEASE WITHOUT ACUTE LESIONS

Case No	Age in Yrs	Service in Mos	Illness in Days	Valve	Wound	Disease	Organism
36	24	19	5	Sclerotic aortic	Belly	Gas gangrene	Perfringens, streptococcus
36	43	18	20	Chronic mitral	Chest	Streptococcus meningitis	No growth
64	24	18	28	Chronic mitral	Head	Staphylococcus meningitis	?
87	29	6	10	Chronic aortic	Thigh	Septicemia	Streptococcus

² Bayne-Jones, S. The Blood Vessels of the Heart Valves, *Am Jour Anat*, 1917, **21**, 449.

CARDIAC HYPERTROPHY

In several of the earlier necropsies it was thought that the heart was enlarged without noticeable cause. Scales were then purchased to try and determine if the life of the soldier induces a cardiac hypertrophy. It was not possible to weigh the cadavers so that the size was indicated as tall, medium or short, in some cases this was neglected.

The average weight of the heart in twenty-four men whose size was not noted was 305 gm. Excluding one heart of 420 gm regarded as definitely hypertrophic, the average was reduced to 300 gm. Nineteen of these men had slight sclerosis of the aorta. The average service was twenty-three months and age 24 years. The average kidney weight 328 gm.

The average heart weight in twenty tall men was 344 gm. Excluding two hearts of over 400 gm, this was reduced to 336 gm. Fifteen of these men had slight sclerosis of the aorta. The average service was twenty-five months and the average age 28 years. The average kidney weight was 374 gm.

The average heart weight in eighteen medium sized men was 322 gm. Excluding three hearts of more than 400 gm, this was reduced to 301 gm. Thirteen of these men had slight sclerosis of the aorta. The average service was twenty months and the age 28 years. The average kidney weight was 346 gm.

The average heart weight in ten small men was 265 gm, none exceeding 400 gm. Five of these men had slight sclerosis of the aorta. The average service was sixteen months and the age 24 years. The average kidney weight was 301 gm.

The foregoing information is summarized in Table 3.

TABLE 3—SUMMARY OF THE STUDY AT NECROPSY OF THE HEARTS
IN A SERIES OF SOLDIERS

Stature	Number of Cases	Heart, Weight in Gm	Excluding Hyper- trophy	Scler- osis	Service	Age	Kidneys Weight in Gm
No note	24	295	300	19	23	24	323
Tall	20	344	336	15	25	28	374
Medium	18	322	301	13	20	28	346
Small	10	265	265	5	16	24	301
Totals	72	314	305	52	22	27	342

INFLUENCE OF ARTERIOSCLEROSIS AND CHRONIC INTERSTITIAL
NEPHRITIS

The importance of the influence of arteriosclerosis and chronic interstitial nephritis was considered and the cases grouped as follows. There were eighteen cases with both arteriosclerosis and chronic interstitial nephritis whose hearts averaged 316 gm in weight,

excluding three cases with hearts of more than 400 gm, the average was reduced to 283 gm. There were thirty-four cases with arteriosclerosis and without chronic interstitial nephritis, the average heart weight being 319 gm, excluding two large hearts, this was reduced to 314 gm. There were only two cases with chronic interstitial nephritis and without arteriosclerosis, too few to present figures. There were fifteen cases without either arteriosclerosis or chronic interstitial nephritis, the average heart weight being 303 gm, excluding large hearts, this was reduced to 295 gm (Table 4 shows this in summary)

TABLE 4—SUMMARY OF THE INFLUENCE OF ARTERIOSCLEROSIS AND CHRONIC INTERSTITIAL NEPHRITIS ON HEART WEIGHTS

With Arteriosclerosis and Chronic Interstitial Nephritis		With Arteriosclerosis, without Chronic Interstitial Nephritis		Without Arteriosclerosis, or Chronic Interstitial Nephritis	
Number of Cases	Average Weight of Heart, Gm	Number of Cases	Average Weight of Heart, Gm	Number of Cases	Average Weight of Heart, Gm
18	316	24	319	15	303
Excluding three large hearts	283	Excluding two large hearts	314	Excluding one large heart	295

As would be expected, the association of these two lesions is accompanied by greater heart weight than is the case when they are absent, but if the large hearts are excluded in making the average it would appear as if the arteriosclerosis were the more important change. Anatomically, the lesions were mild in both the cases of arteriosclerosis and chronic interstitial nephritis. Without functional studies of the cardiovascular system and renal sufficiency and with the variance in figures a conclusion is unjustified. No light was thrown on the variance of these figures by examining the age, service and stature of these cases, as the distribution was fairly even.

INFLUENCE OF AGE AND LENGTH OF SERVICE

The question of age and service was investigated taking the average of all the cases as the dividing line. There were thirty-six patients more than 27 years old with an average heart weight of 326 gm, excluding five large hearts, 300 gm, in contrast to thirty-four patients less than 27 years of age with an average heart weight of 305 gm, excluding one large heart, 301 gm. There were thirty-four patients with more than twenty-two months' service with an average heart weight of 350 gm, excluding three large hearts 324 gm, in contrast to thirteen patients less than 27 years of age and with less than twenty-two months' service, with an average heart weight of 279 gm, not including any large hearts. Table 5 gives a summary of these cases.

TABLE 5—SUMMARY OF THE RELATION OF AGE AND LENGTH OF SERVICE IN THEIR EFFECT ON HEART WEIGHTS

Over 27 years old	326 gm	Under 27 years	305 gm
Excluding five large hearts	300 gm	Excluding one large heart	301 gm
Over twenty two months' service	330 gm	Under twenty two months' service	293 gm
Excluding four large hearts	316 gm	Excluding two large hearts	284 gm
Over service and age	350 gm	Under service and age	279 gm
Excluding three large hearts	324 gm	No large heart	

It will be noted that, excluding the large hearts, there is no difference in weight in the two age periods, but that under the same condition the men who have served more than twenty-two months have hearts averaging 32 gm heavier than their fellows of shorter service. In the case of thirteen men who were more than 27 years of age and



Fig 1 (Case 21)—Aortic valve showing vegetations just above the line of closure. This case also had acute mitral disease.

had more than twenty-two months of service, the hearts averaged 71 gm greater in weight than in the case of thirteen others who were less than 27 years of age and had less than twenty-two months' service, excluding large hearts the difference in the two groups was 45 gm. The stature of these men was considered, but appeared to be fairly evenly distributed. It, therefore, appears that long service and increased heart weight go hand in hand. If to the long service there is added greater age, the increase in weight becomes more marked.

Hearts weighing 400 gm or more have been regarded as examples of hypertrophy and deducted from the total in reaching averages. Six hearts fell in this group and all but one could be accounted for by

other lesions in the body. Three of these were associated with chronic interstitial nephritis, which although of mild degree may have been sufficiently diseased functionally to have produced high blood pressure. All of these showed in addition a slight sclerosis of the aorta. One case showed the abnormality below the aorta as described elsewhere, which might easily have led to hypertension and in addition a slight sclerosis of the aorta. One other case showed only arteriosclerosis as a possible cause for the hypertrophy. The patient (Case 69) had a heart of 420 gm with no arteriosclerosis, no valve lesion, no chronic nephritis or any other apparent cause of enlargement. His body is described as that of a "tall, heavily built, well nourished man." He had a liver of 2,685 gm, showing passive congestion, a soft flabby spleen of 285 gm, apparently normal kidneys weighing 410 gm. He was a Scottish guardsman.



Fig 2 (Case 10)—Aortic valve showing erosion and vegetations. (corpus Arantii)

served thirty-six months. Compared to the weight of the other hearts the heart is not materially enlarged and doubt is left in one's mind as to whether or not this case should be classified as a hypertrophy.

When it is noted that the greatest weight recorded in the series was 475 gm and that next to that are two hearts of 420 gm, one being a doubtful hypertrophy, it can be seen that definite hypertrophy of the heart played a very small part in the gross morbid anatomy of these soldiers.

These six cases averaged 37 years of age and twenty-seven months of service, distinctly above the average of 27 years of age and two months' service. This may be taken to support the suggestion that older men of long service tend to have larger hearts than the opposite group.

TABLE 6—SUMMARY OF THE FINDINGS AT NECROPSY IN SIX CASES
CLASSED AS HYPERTROPHY OF HEART

Case No	Age in yrs	Service in mos	Heart Wt, Gm	Valve Lesion	Sclerosis Aorta	Kidney Wt, Gm	Kidney Lesion	Disease	Stature
14	29	36	420	Acute aortic mitral valvulitis	+	430	Chronic interstitial nephritis	Streptococcus septicemia	No note
46	26	32	410	None	—	420	Cloudy swelling	Streptococcus meningitis	Tall
51	33	15	400	Abnormal acute aortic	+	356	Cloudy swelling	Streptococcus septicemia	Medium
54	48	27	475	None	+	340	Chronic interstitial nephritis	Gangrene	Medium
56	45	18	400	Sclerotic mitral	—	450	Chronic interstitial nephritis	Chest wounds	Medium
69	40	36	420	None	—	410	Normal	Chest wounds perfringens	Tall

ARTERIOSCLEROSIS OF THE AORTA

This condition was noted in sixty-two of a total of eighty-one cases in which a note was made on the aorta. This was practically always slight, appearing usually as narrow white firm streaks longitudinally arranged throughout the length posteriorly, resembling a little the streaks of fatty change seen in the aortas of children dying from acute infection but being white and definitely fibrosed. A few of these showed slight fatty changes, but none showed definite calcification. It is not likely that this change can be accounted for by the acute infections from which the men died, it seems more reasonable to attribute the change to some other cause.

Coronary sclerosis was present in five cases, one of which showed also a sclerosis of the mitral valve. Sclerosis of the cerebral arteries was noted in one case of seventy-seven cases examined.

Averages were estimated of the age and term of service of sixty-two patients who showed sclerosis of the aorta and nineteen patients who failed to show it and the resulting figures were the same in each, namely, 27 years of age and twenty-two months' service. It is therefore unlikely that army service or the age of the soldier played any important part in the occurrence of the arteriosclerosis and that its cause must be sought elsewhere.

SUMMARY AND CONCLUSIONS

In summary, it may be stated that in spite of the fact that soldiers represent a group of men selected for superior physique, acute valvular

litis is an important complication of septicemias and pyemias following war wounds. The men developing this complication are somewhat older and of longer service than the average of the entire group studied. The situation of the wound has little to do with this complication, except that wounds of joints form a larger percentage in the group of acute valvulitis cases than is true of the entire group. The *Streptococcus pyogenes* is an important organism, but is not more frequent in the smaller than in the entire group of cases. In one case embolism of the valve vessels seems to have been a cause, and in one



Fig 3 (Case 51)—Aortic valve showing vegetations as indicated by the upper arrow and anomaly as indicated by the lower arrow

other it is a possible cause. The aortic leaflets are the most commonly affected and at the same time show the least marked lesions.

The weight of the heart appears to be greater in men of long service and in older men, the difference being accentuated in men when greater age and longer service coincide. It is therefore tentatively concluded that long service in the army probably leads to an increase in the weight of the heart, and that this change is more marked in men above the average age of this series of soldiers.

It cannot be demonstrated that the life of the soldier leads to the development of arteriosclerosis.

LIST OF CASES OF ACUTE VALVULITIS

I ACUTE AORTIC VALVULITIS

CASE 10 (FIG 2)—The patient, aged 43, had been in the service thirty-three months. He was admitted to the casualty clearing station with shell wound of the buttock and fracture of the great trochanter. He was ill thirty-one days, a large abscess of buttocks developed and five days before death a dry pleurisy of the left side. The necropsy was performed fourteen hours after death and revealed extensive suppuration of thigh extending up to origin of psoas major but not involving hip joint. The heart was soft and flabby with normal valves except that one aortic leaflet showed in the middle of the ventricular surface a small erosion surrounded by very minute soft white vegetations. There was also acute fibrinous pleurisy, acute purulent bronchitis, septic infarct of lung, acute splenic hyperplasia, cloudy swelling of kidneys. Direct smear from psoas muscle showed only streptococci in unusually long chains. Direct smear from septic infarct showed a mixture of organisms, the streptococcus predominating.



Fig 4 (Case 76)—Mitral valve showing vegetation as indicated by the arrow, chordae tendineae enmeshed in vegetation

CASE 12—The patient, aged 22, had been in the service nineteen months. He was admitted to the casualty clearing station with shell wound of the buttock involving the sciatic nerve, with inability to extend the toes. During an illness of fifty days hemorrhage occurred, also edema of the thigh, and extensive suppuration of the thigh involving the left hip joint and following the psoas major to within 4 cm of the diaphragm. At necropsy, fifteen and one-half hours after death, the heart was "small, soft and flabby with pallid friable muscle, the aortic leaflets revealed numerous extremely minute soft white vegetations along the line of closure, other valves normal." There was acute fibrinous pleurisy, bronchopneumonia, cloudy swelling of liver, hyperplasia of splenic follicles, acute pseudomembranous colitis and acute hemorrhagic nephritis. Cultures from the heart blood showed *Streptococcus pyogenes*.

CASE 25—The patient, aged 34, had been in the service twenty-five months. He was admitted to the casualty clearing station with shell wound of the hip grooving the great trochanter. During an illness of sixteen days all the symptoms of a septicemia developed. At the necropsy, four hours after death, the heart "weighed 220 gm and was normal except for the presence of a pinhead-sized vegetation on the right posterior leaflet of the aortic valve immediately below the corpus Arantii." There was also marked suppuration of thigh, passive congestion, edema and healed tuberculosis of lungs, cloudy swelling of the liver, submucous petechiae of stomach, follicular and general acute splenic hyperplasia and acute nephritis. Cultures from the heart blood were contaminated.

CASE 30—The patient, aged 28, had been in the service thirty-six months. He was admitted to the casualty clearing station with a penetrating shell wound of chest. During an illness of twenty-two days pneumothorax developed, also hemothorax, phlebitis of right leg, purulent peritonitis, and from the chest a pure culture of *Streptococcus pyogenes* was obtained. At the necropsy, thirteen hours after death, the heart "weighed 345 gm, was soft and flabby and shows moderate dilatation of right side, the left posterior leaflet of the aortic valve revealed on the left half of its line of closure two pinhead-sized white fairly firm vegetations fairly well attached." There was also bilateral acute



Fig 5 (Case 20)—Mitral valve showing vegetations as indicated by the arrows

fibrino-purulent pleurisy, hypostatic pneumonia, acute purulent peritonitis (metastatic) marked cloudy swelling of liver, acute hyperplasia of spleen with multiple infected infarcts and acute nephritis. Direct smears from the right pleura and belly showed numerous long chains of gram-positive streptococci which were outgrown in cultures by contaminations. This case is regarded as a streptococcus pyemia.

CASE 5 (FIG 3)—The patient, aged 35, had been in the service fifteen months. Admitted to the field ambulance with extensive shell wound of left shoulder. During an illness of seventeen days gas gangrene developed, and the left upper extremity was amputated. At necropsy, seven hours after death, the heart "weighed 400 gm, showed considerable dilatation of right side, contained firm clot and frothy blood, aortic leaflets showed numerous extremely minute soft white vegetations along the line of closure, other valves normal, extending from the junction of the large mitral leaflet and left posterior aortic leaflet to a point on the septum just below the right posterior aortic leaflet was a band of fibrous tissue 2 mm in thickness and about 15 mm long, which widened in the middle to form a generally spherical sac about 7 mm in diameter with an opening about 4 mm in diameter, the septal end of this band was continued in a heavy band of muscle about 4 mm in diameter not completely separated from the septum and extending vertically downward for 2.5 cm." The other organs showed the usual changes of gas gangrene. From the heart blood there were isolated *Streptococcus pyogenes* and *Bacillus perfringens*.

II ACUTE MITRAL VALVULITIS

CASE 7—The patient, aged 23, had been in the service twenty-two months. He was admitted to the casualty clearing station after "lying out" four days with shell wounds of left leg, left wrist and back, without any evidence of gas gangrene. He was ill seven days and died suddenly. The necropsy was performed eighteen hours after death and showed in addition to the wounds an acute suppurative inflammation of the left knee joint. There was no evidence of thrombosis or embolism in the femoral veins, coronary, pulmonary or cerebral arteries. The heart was described as "somewhat soft and flabby, showing no dilatation of the left side but marked dilatation of entire right side, both sides filled with firm current jelly clot, on the posterior leaflet of the mitral valve at its line of closure were three minute, white, soft, acute vegetations." There was passive congestion of the lungs, cloudy swelling and passive congestion of the liver, acute splenic hyperplasia and acute hemorrhagic nephritis. From the knee joint there was isolated the *Streptococcus pyogenes*.

CASE 76 (FIG 4)—The patient, aged 20, had been in the service sixteen months. He was admitted to the field ambulance with shell wound of back. At the casualty clearing station he had hematuria and vomiting, abdominal

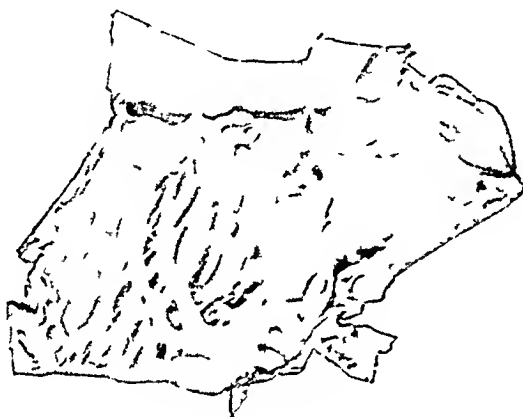


Fig 6 (Case 2)—Pulmonic leaflets showing massive vegetation

section revealed no visceral injury but retroperitoneal and intraperitoneal hemorrhage. At the base a retroperitoneal abscess was opened and drained followed by left empyema. He died after an illness of ten days. At necropsy, twenty hours after death, it was found that the wound had penetrated the lower part of chest and had split the lower pole of the left kidney. "Heart weighed 235 gm, showed a firm musculature and appeared to be normal except that the auricular surface of the right half of the posterior mitral leaflet was practically covered by a mass of small vegetations, soft, loosely adherent and salmon colored, the neighboring part of anterior leaflet showed a similar vegetation 2 mm in diameter, other valves, coronaries and foramen ovale were normal." There was also a left sided empyema, acute purulent bronchitis, cloudy swelling of liver and kidneys, follicular hyperplasia of spleen and wound of kidney with practically no suppuration. Cultures from the heart blood revealed pure growth *Streptococcus pyogenes*.

III ACUTE PULMONARY VALVULITIS

CASE 2 (FIG 6)—The patient, aged 22, had been in the service twenty-four months. He was admitted to the casualty clearing station with shell wounds of left thigh, left ankle, left buttock and face. At the base hospital it was found that the ankle wound penetrated the ankle and tarsal joints and the

thigh wound was associated with a fracture of the femur. He was ill twenty-nine days, during the course of which an abscess of left arm developed, also two abscesses of the thigh, cellulitis of the left ankle and bed sores. The necropsy was performed twenty hours after death and the heart was described as follows: "of about normal size, soft and flabby, shows slight general dilatation, all valves normal except the pulmonary, all three leaflets of which show on the ventricular surface extensive flat, white, soft, easily detachable vegetations covering the entire leaflet and extending slightly onto the wall of the septum, and showing three minute vegetations on the intima of the pulmonary artery." There was associated miliary abscesses of the lungs, bronchopneumonia, cloudy swelling of liver, acute splenic hyperplasia and acute nephritis. From the lung abscesses there was isolated the *Streptococcus pyogenes* and a staphylococcus.

IV ACUTE TRICUSPID VALVULITIS

CASE 9 (FIG 7)—The patient, aged 29, had been in the service twelve months. He was admitted to the casualty clearing station with "inflammation of connective tissue" of left foot and doubtful pleurisy of left side. At the



Fig 7 (Case 9)—Tricuspid valve showing triangular ulceration in the posterior cusp

base hospital it was found that the "inflammation of connective tissue" had followed a blister of the left instep developing on a long march. He was ill twenty-eight days, developing cellulitis of entire left lower extremity with inguinal lymphadenitis, left subacromial bursitis and multiple subcutaneous abscesses. The necropsy was performed fourteen hours after death and revealed in addition to the above features, acute suppurative inflammation of the ankle joint particularly at the astragalo-scapoid junction and gangrene of the great and second toes. The heart was "soft and flabby with pallid muscle, normal valves except that the posterior leaflet of the tricuspid valve showed, near its attachment to the ring, a horizontal linear abscess 10 by 2 mm in the substance of the valve, over which the auricular surface showed a group of minute, soft, white vegetations covering an area 4 by 5 mm." The lungs revealed one hemorrhagic infarct and a large number of small septic infarcts and abscesses, some of which are partially encapsulated, local acute fibrinous pleurisy, cloudy swelling and passive congestion of liver, acute hyperplastic nephritis, acute suppurative nephritis, occluding thrombo-phlebitis of left femoral veins. The heart blood showed pure culture of *Staphylococcus pyogenes aureus* and this organism predominated in direct smears from abscesses in lungs, kidneys, thigh wound and thrombus of vein.

V ACUTE AORTIC AND MITRAL VALVULITIS

CASE 14—The patient, aged 29, had been in the service thirty-six months. He was admitted to the casualty clearing station with shell wound and compound fracture of the right thigh, and superficial wounds of the leg, abdomen, chin and head. During an illness of seven days signs of fracture of the skull and pneumonia developed. At necropsy, eleven hours after death, "the heart weighed 420 gm, showed a thick, firm left ventricle and moderately dilated right side, the mitral leaflets showed numerous small clusters of minute, white, soft, firmly attached vegetations extending along the line of closure, the aortic leaflets showed less numerous similar vegetations along the line of closure particularly marked on the left posterior leaflet." The skull showed fracture with extensive subdural hemorrhage, the lungs acute purulent bronchitis and extensive confluent bronchopneumonia, the liver cloudy swelling and fatty metamorphosis, the kidneys cloudy swelling superimposed on slight chronic interstitial nephritis. Cultures from the heart blood showed pure growth *Streptococcus pyogenes*.



Fig 8 (Case 75)—Mitral stenosis showing superimposed acute vegetations

CASE 21 (FIG 1)—The patient, aged 21, had been in the service sixteen months. He was admitted to the casualty clearing station with shell wounds penetrating right elbow joint, right knee joint and buttock. During an illness of thirteen days the patient developed infection of knee and elbow joints and finally a meningitis. At necropsy, twelve hours after death, the "heart weighed 300 gm, was markedly dilated on the right side, the aortic leaflets showed very minute soft white vegetations along the line of closure, the posterior leaflet of the mitral showed four such vegetations at the middle of the line of closure, left ventricular muscle was firm, and heart was otherwise normal." There was also acute purulent cerebral meningitis, passive congestion of lungs, liver and kidneys and slight chronic interstitial nephritis. Cultures from the brain and the heart blood showed pure growth *Streptococcus pyogenes*.

CASE 40—The patient aged 36 had been in the service eighteen months. He was admitted to the field ambulance with shell wound of the right leg, left knee and right arm. During an illness of four days clinical signs of a streptococcus septicemia developed and gas gangrene of right leg for which an amputation was made in mid thigh. At the necropsy fourteen hours after death the heart "weighed 365 gm. was of doughy consistence with epicardial congestion and hemoglobin staining of the endocardium. anterior and right posterior leaflets of aortic valve showed several red soft very minute vegetations on the corpora Arantii extending slightly along the lines of closure. similar vegetations were found at the right junction of the mitral leaflets approximately in the position of the line of closure." There was also gas gangrene of the right thigh with the incident softening of all the organs and a chronic interstitial nephritis. Cultures from the heart blood showed no aerobic growth anaerobically *Bacillus perfringens* was found.

VI ACUTE SUPERIMPOSED ON CHRONIC VALVULITIS

CASE 20 (FIG 5)—The patient aged 34 had been in the service thirty-five months. He was admitted to the casualty clearing station with shell wounds of the right buttock and left elbow. During an illness of fourteen days there were two hemorrhages from the buttock wound and bloody stools (no perforation of the gut). At necropsy two and a half hours after death the heart weighed 320 gm. and showed marked dilatation of the entire right side with slight hypertrophy of the left auricle. mitral valve showed fibrosis, adhesion, slight retraction of leaflets and adhesion with slight shortening of chordae tendineae. along the line of closure were numerous millimeter-sized soft light yellow vegetations. the stenosis was moderate, the orifice measuring 6.5 cm. the aortic leaflets were normal except that along the line of closure of each leaflet there were a few vegetations similar to those on the mitral valves of the right side were normal. There was, in addition, generalized icterus, acute splenic hyperplasia with multiple hemorrhagic infarcts, acute nephritis, acute fibrinopurulent pelvic peritonitis, acute pseudomembranous enterocolitis. Cultures from the heart blood showed pure growth *Staphylococcus pyogenes aureus*.

CASE 75 (FIG 8)—The patient aged 37 had been in the service thirty-six months. He was admitted to the casualty clearing station with superficial wound of chest and penetrating wound of pelvis not involving the gut. During an illness of eight days signs of pneumonia developed. At necropsy four hours after death the heart "weighed 350 gm. and showed slight hypertrophy of the left auricle. the mitral leaflets were thickened somewhat retracted and adherent, associated with thickening and adhesion of the chordae tendineae, at the right junction of the leaflets on the auricular surface was a mass of dark brown soft firmly adherent acute vegetations 5 mm in diameter. aortic leaflets were diffusely thickened, not retracted but showed adhesion of right posterior and anterior leaflets as far as the corpora Arantii associated with stiffening and calcification. other valves, coronary arteries and foramen ovale were normal." There was also multiple septic intarction of the lungs, bronchopneumonia, acute fibrinous pleurisy, acute splenic hyperplasia and embolic abscesses of the kidneys. Cultures from the heart blood showed pure growth *Staphylococcus pyogenes aureus*.

PATHOLOGIC REPORT ON FORTY-THREE CASES OF ACUTE POLIOMYELITIS *

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The morbid anatomy of acute poliomyelitis has received careful and painstaking study by a number of European pathologists

Rissler¹ was the first to describe the anatomic changes in the central nervous system, with a report of three cases, in 1888. The changes described were confirmed by a number of other students of the disease, chief among whom are Wickman² with a report of fourteen cases, Harbitz and Scheel³ with nineteen cases, and Strauss⁴ with eight cases.

These anatomic studies are confined chiefly to the nervous elements of the body, comparatively little attention having been paid to the other organs. Flexner, Peabody and Draper⁵ studied eleven acute cases with special reference to the changes in the organs other than the central nervous system. They found constant changes in the lymphatic structures throughout the body and called attention to focal degenerative lesions in the liver. The changes in the lymphatic tissues consisted chiefly of hyperplasia of the reticular and endothelial cells.

Though the changes in the central nervous system of acute poliomyelitis as described by Rissler have been confirmed by all subsequent workers in this field, two schools of opinion have developed as to the interpretation of these changes. One group, headed by Rissler, believes that the nerve cell destruction is the primary change and that the cell reaction or inflammatory change has been called forth by the presence of the virus in the affected part. Monckenberg⁶ and Cassierer⁷ agree with Rissler, inasmuch as they have studied cases in which there were marked nerve cell destruction with a minimum of interstitial reaction. Wickman,² Harbitz and Scheel³ and others consider that the interstitial process is the primary stage and that the nerve cell

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* From the Bureau of Laboratories, Department of Health.

* This report was ready for publication in January, 1917, but was delayed on account of technical difficulties. In the series of articles on Poliomyelitis in THE ARCHIVES, September, 1917, a part of the first article was incorrectly headed Part II, Pathologic Studies.

1 Rissler, John. Nord Med Ark, 1888.

2 Wickman, Ivan. Nervous and Mental Disease Monograph, Series 16.

Harbitz and Scheel. Deutsch med Wchnschr, 1907, p 48.

4 Strauss, J. Arch Pediat, August, 1910.

5 Flexner, Peabody and Draper. Jour Am Med Assn, 1912, 58, 109.

6 Monckenberg, J. Munchen med Wchnschr, 1903.

7 Cassierer. Neurol Centralbl, 1898.

degeneration is secondary to the interstitial changes Wickman has never found ganglion cell destruction without interstitial lesions On the other hand, he has found interstitial changes without nerve cell degeneration Harbits and Scheel state further that the disease is a blood borne infection, the virus lodging first in the meninges, and that it spreads from this site to the nervous tissue proper

Forssner and Sjoval⁸ first called attention to the importance of neurophagocytosis in the production of the histologic picture of this disease

The epidemic of the summer of 1916 furnished the opportunity for the postmortem study of forty-three patients who had acute poliomyelitis, forty-one of whom died in the acute stage Thirty-five were cases from the Willard Parker Hospital, and six were in private residences Material⁹ from two were sent to the laboratory for diagnosis Eight cases other than poliomyelitis came to the necropsy table from the poliomyelitis wards Four of these proved to be tuberculous meningitis, one lobar pneumonia, one congenital heart disease, one purulent pericarditis, purulent pleuritis, bronchopneumonia and general pyemia, one, intracranial hemorrhage

The poliomyelitis cases as to sex, age and duration of illness are divided as follow

Age	Number
Up to 1 year	8
1 to 2 years	8
2 to 3 years	13
3 to 5 years	2
5 to 10 years	4
10 to 16 years	1
Over 16 years	5
Up to and including 5 years, there was a total of 31 or 75.5 per cent	
Males, 28, females, 13	

Duration of Illness	Number
3 days	10
4 days	5
5 days	6
6 days	5
7 days	5
8 to 11 days	4
Over 12 days	4
Undetermined number of days	2

Thirty-one, or 75.5 per cent of the patients died within the first week after onset

The clinical classification as to types is based on the evidence of anatomic lesions Thus, all cases exhibiting involvement of the lower motor neuron were called spinal cases These were again divided

⁸ Forssner and Sjoval *Ztschr f klin Med*, 1907

⁹ No history obtained of sent-in cases

TABLE OF GROSS AND MICROSCOPIC CHANGES

No	Name	Sex	Age in Years	Duration of Illness Days	Type of Case	Gross Changes					Microscopic Changes					Remarks
						Brain	Cord	Mes Node	Peyer's Patches	Spleen	Brain	Cord	Mes Node	Peyer's Patches	Spleen	
1	R S	♀	1 6/12	11	Ascending spinal	++	++	+	?	++	++	++	+	+	+	
2	R X	♀	1 1/12	7	Upper spinal	+	+	—	—	—	+	++	—	—	—	
3	G B	♀	1 7/12	6	Upper spinal	+	+	+	±	+	+	+++	+	+	+	
4	M F	♂	2 6/12	3	Upper spinal	+	—	?	+	—	+	++	+	+	+	
5	C P	♂	8/12	6	Ascending spinal	++	?	—	+	+++	+	+	+	+	+	
6	J N	♂	2 6/12	3	Upper spinal	++	+	+	±	+	+	++				
7	I S	♂	3	4	Upper spinal	++	+++	+	+	++	±	+	—	—	—	
8	M L	♀	15 6/12	5	Ascending spinal	+++	?	—	—	—	+	+				Partial necropsy
9	E C	♂	7/12	6	Ascending spinal	±	+	+	+	—	+	+	+	—	—	
10	M D	♂	2 6/12	7	Upper spinal	+	+	++	+++	—	+	+	+	+	+	
11	I F	♂	2	5	Upper spinal	++	++	—	—	—	+	+				Partial necropsy
12	G W	♂	21	9	Ascending spinal	+	++	—	—	—	+	++	—	—	—	
13	N H	♀	1 11/12	10	Ascending spinal	++	++	+	+	—	+	++	—	—	+	
14	A L	♂	2	7	Ascending spinal	+-		—	?	+++	+	++	—	—	+	
15	A R	♂	8	4	Cortical	++		++	++	—						Sections lost
16	A L	♀	2 6/12	?	Upper spinal	+		—	++	—	+	++	±	±	±	
17	I N	♂	8/12	28	Upper spinal	±		—	—	—	±	±	—	—	—	Died of acute gastro enteritis
18	M K	♀	6	7	Ascending spinal	+		+	?	—	+	+	+	+	+	
19	E A	♂	32	5	Ascending spinal	+	+	—	—	+	+	++	—	—	+	
20	H V	♂	7/12	? 7	Ascending spinal	+	±	±	+	+	+	+++	±	+	+	Diffuse infiltration predominates

21	S. G.	♂	0/10	3	Upper spinal	1	1	1	?	1	1	1 1	1	1	1	
22	A. K.	♀	1	1	Upper spinal	1	.	1	1	1	1	1 1	1	1	1	
23	R. C.	♀	1	5	Menigitis	1		?	—	1	1	1	—	—	1	
24	R. S.	♀	1	3	Upper spinal	1		1	1	1	.		.	.		Sections lost
25	S. R.	♀	1 5/10	1	Upper spinal	1	1	1	?	1	1	1 1	—	—	2	
26	L. S.	♀	1 0/10	1	Ascending spinal	1 1	1	1	1	1	1	1 1				
27	A. K.	♀	0/10	0	Menigitis	1		—	—	—	.	.				Sections lost
28	M. G.	♂	0/10	11	Upper and lower spinal	1	..	.	1	1	1	1 1	1	1	1	Labial pneumonia
29	G. G.	♂	1 0/10	1	Upper spinal	1	.	1	?	1	1	1 1	1	—	1	
30	P. C.	♂	1	0	Ascending spinal	1	.	.	—	1	1	1 1	—	—	—	
31	S. G.	♂	1 0/10	1	Upper spinal	.		1	1	1	1	1 1	.	—	1	
32	K. V.	♂	1	3	Ascending spinal	1	?				1	1 1 1				
33	H. V.	♂	0/10	1	Upper spinal	1	.	?	—	.	.	1	—	—		
34	P. S.	♂	1	?	Upper spinal	1	.		1	—	1	1	1	1	1	Marked on admission
35	R. P.	♂	2/10	1	Ascending spinal	1	1			1	1	1	—	—	—	
36	L. K.	♂	27	5	Cerebral	1 1	1	?	?	—		..			.	Sections lost
37	H. M.	♂	5 0/10	5	Upper spinal	1	1	1	1		1	1	1	1	1	
38	J. A.	♂	1	1	Ascending spinal	1	1	—	.	1	1	1	—	—	1	
39	G. B.	♂	68	11	Menigitis	1	.		.		1 1 1	1			.	Partial necropsy
40	A. A.	♂	1 2/10	1	Upper spinal	1	1		1	1	1	1	—	1	1	
41	W. G.	♂	?	?	?	.			.			1 1	?	?	?	Cord only was sent to laboratory
42	H. B.	♂	?	?	?		..					1 1	?	?	?	Cord only was sent to laboratory
43	H.	♂	0	10	Menigitis	1	1				1	1	.			Only cord and brain examined

1 Exploratory change, . no pathologic change, 1 — slight change, 1 — distinct change, 1 1 — marked pathologic change, 1 1 1 — very marked pathologic change.
 1 Necropsy at home, 1 Place of necropsy unknown or none had. In all other cases necropsies at Willard Parker Hospital.

into two classes one in which the process begins in the lumbosacral cord and progresses upward involving the arm and respiratory centers, and the other, in which the process begins in the cervical and bulbar regions or in the gray matter from which the cranial nerves have their origin. Those cases exhibiting disturbance of upper motor neuron or other disturbance of the sensorium belong to the cortical type. Those cases showing only marked meningeal symptoms were considered to be of the meningitic variety. They are as follows:

Type of Cases	Number
Ascending spinal	17
Upper spinal	18
Cortical	2
Meningitic	4

In one of the ascending spinal cases the patient survived the poliomyelitis infection and died of lobar pneumonia thirty-four days after the onset of illness. Another patient belonging to the upper spinal group, died of acute gastro-enteritis twenty-eight days after the onset of the poliomyelitis infection.

The gross changes when in the brain were chiefly those of varying grades of congestion of the pial and parenchymatous vessels, of edema of the pia and brain substance. In a few instances, the brain tissue was of softer consistency than normal. One brain, in a man of 27 years, besides intense congestion and edema, presented extreme softening in one hemisphere involving the motor area and a great portion of the parietal lobe in which lies the sensory area. Clinically, this man presented a hemiplegia and hemianesthesia of the opposite side. The brain tissue was reduced to mushy consistency with multiple hemorrhagic flecks throughout the cut surface. No gross hemorrhage was visible and the spinal fluid was clear, with changes such as one would find in poliomyelitis. The Wassermann was negative. This is the only cortical case of simulating apoplexy that came under observation at the Willard Parker Hospital among a great number of cases. The changes in the spinal cord were observed mainly on cut sections through the pons, medulla and upper cervical portion, it being our intention to preserve as much as possible of the material in a clean state for cultures, microscopic study and animal experimentation. The cut sections presented degrees of hyperemia and swelling of the gray matter. The gray "H" bulged above the level of the surrounding white matter and was sharply demarcated from same. In marked cases, the gray matter was simply pink tinged and easily marked off from surrounding white matter. Sections through normal cords fail to show the ready differentiation between gray and white matter which is to be observed in cords from poliomyelitis infection. In some cases

the edema involved the white matter as well and appeared to soften the cord as a whole

The heart and lungs showed no striking changes, except that practically all of the lungs presented acute edema and congestion incident to the paralysis of respiration

The liver and kidneys showed varying degrees of acute congestion, and in some cases, parenchymatous degeneration

Particular attention was paid to the lymphatic structures, as some observers contend that lymphoid tissue plays a considerable rôle in the pathologic picture of acute poliomyelitis. The lymphoid structures of the small intestines, the Peyer's patches and solitary follicles, in a number of instances, were considerably raised and reddened. There were no indications of ulceration. The mesenteric lymph nodes were enlarged and reddened. The spleen, in many cases, showed marked congestion and more or less prominence of the malpighian bodies

Following is a tabulation of gross changes as described in the foregoing

	Present	Absent	Not Noted or Examined
Brain	35	5	
Cord	20	5	15
Intestine	16	8	16
Mesenteric nodes	19	10	11
Spleen	18	16	6

A number of the necropsies were granted only for the examination of the brain and cord, and this fact accounts for the incompleteness of the data as to the other organs

The microscopic pictures of the central nervous system in this study correspond closely with those described by Rissler, Wickman and Harbitz, and Scheel. The disease process involves all the elements that enter into the makeup of the central nervous system

The pia mater in most cases was affected most severely in that portion which is opposed to the most severe process in the subjacent cord. Thus, in the ascending spinal type the most marked changes are to be found in the pia of the lumbosacral region, whereas in the upper spinal type the severest changes will be found in the pia of the upper cord, medulla or pons. However, quite a number of sections presented intense round cell infiltration of the cord proper, whereas the pia of the corresponding level showed little or no cell invasion. These changes consist of congestion of the blood vessels, round cell infiltration of varying degree, both around the blood vessels and also diffusely in the interstitial tissue and edema, all of which produces a thickening of the membrane. Of the thirty-nine cases, only two failed to show infiltrative changes in the pia of the cord in any of the sections studied. In six, these changes were very slight, consisting mainly of

congestion and a slight degree of perivascular infiltration. Two of these were seven and five day upper spinal cases. In the five day case, lesions were found only in the pons and medulla. In one of the remaining cases the inflammatory changes both in the pia and cord proper were slight, but the extent of nerve cell destruction was out of proportion to that of the inflammatory process. In another case, while there was only a considerable degree of congestion and edema

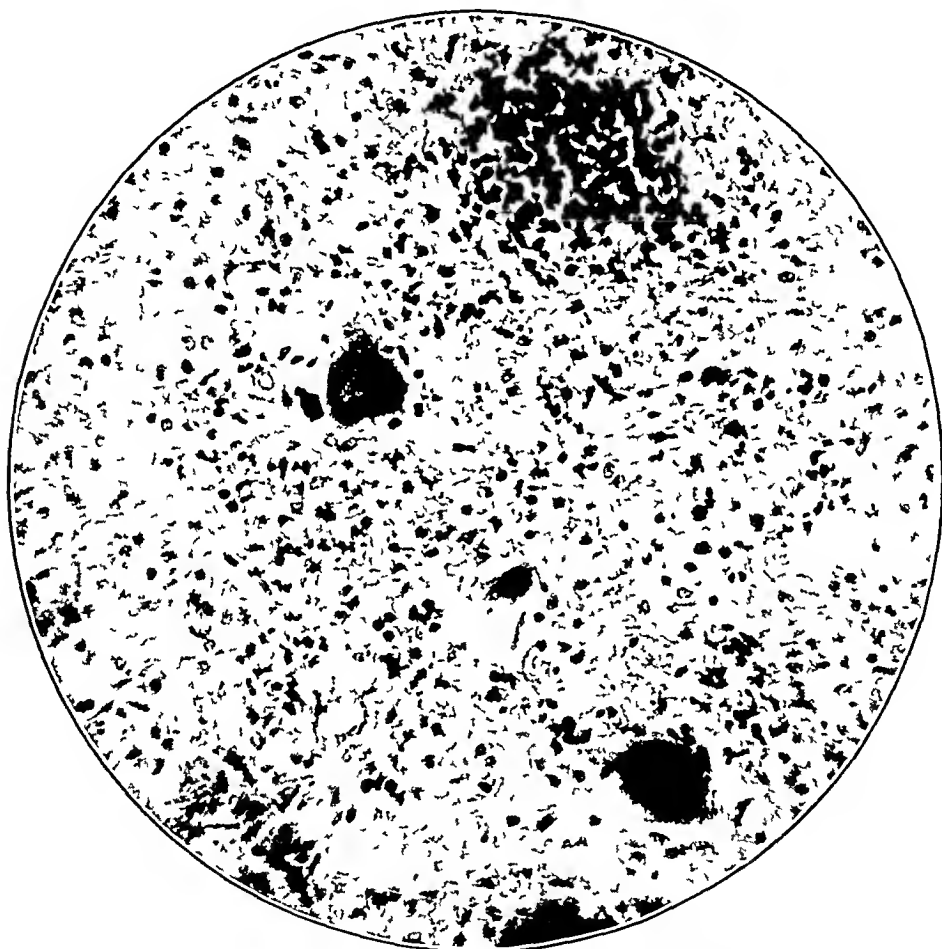


Fig 1—Cord showing considerable round cell infiltration. Two of three nerve cells are fairly well preserved. One of these, however, shows early phagocytosis.

of the pia without cellular infiltration, the gray matter was densely infiltrated with cells.

The pia of the brain and cord presented changes varying from simple congestion and edema to a marked degree of cellular infiltration and thickening of the membrane.

SPINAL CORD

The spinal cord presented changes of the most severe type usually in that part of its extent that was diseased as indicated clinically by the flaccid paralysis, usually in the lumbar and cervical enlargements.

These changes consist of varying degrees of perivascular infiltration, diffuse interstitial cellular infiltration of the gray matter and occasionally of the white matter, of degeneration and phagocytosis of the ganglion cells most marked as a rule in the anterior horns and some degree of edema. Ten of thirty-nine cases examined exhibited hemorrhage in one or both anterior horns. Cords in which hemorrhage occurred presented evidences thereof at all levels in varying degree. The gray matter was particularly affected. Ganglion cells were severely damaged. There was however, little or no round cell infiltration. There was marked edema. The most marked ruptures occurred in the anterior horns and in one the horn was almost completely

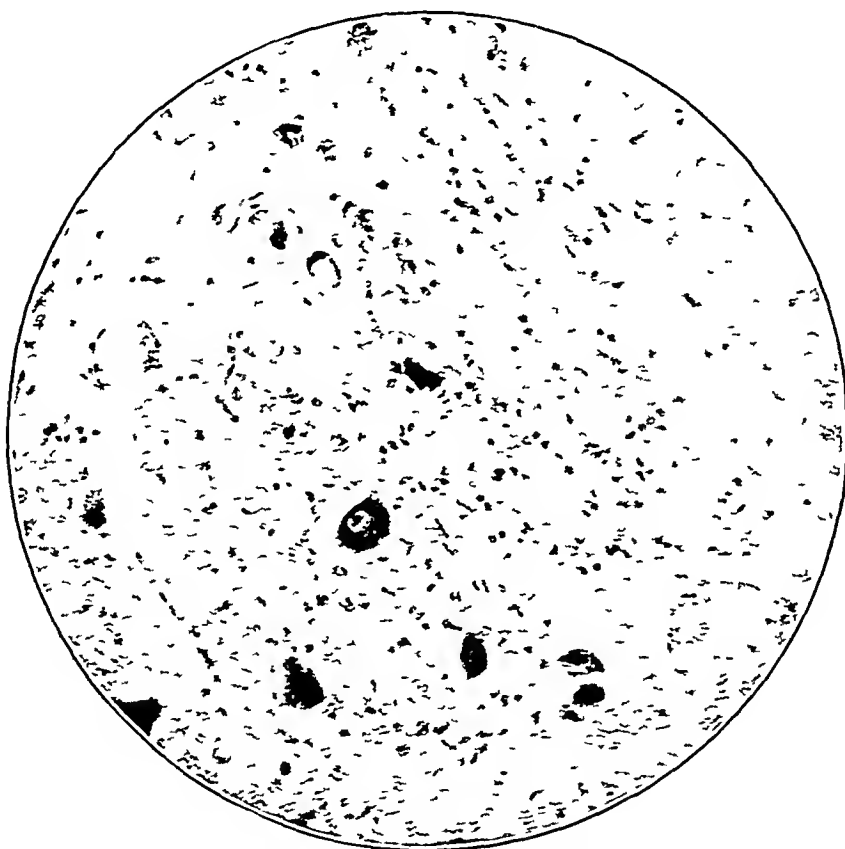


Fig. 2—Section of cord, marked nerve cell degeneration without round cell infiltration

destroyed by the extravasation. Fibrin deposit or other evidence of thrombosis was not noted in any of the vessels.

The perivascular infiltration is most marked as a rule about the vessels in the anterior and posterior median fissures, and in the vessels of the tips of the horns. The vessels of the horn proper seldom show a marked degree of perivascular infiltration whereas the two vessels, one on each side of the central canal while they exhibit extreme dilatation and congestion have not presented infiltration in any of the cases studied thus far.

The most intense diffuse infiltration is usually to be found in the anterior horns. In most of the cases studied, however, the whole of the gray matter participated, sometimes more on one side than another. In one case the posterior horn showed the greater cellular infiltration. It was noted, too, in a number of cases that where the diffuse interstitial infiltration was marked, the perivascular change was less marked and vice versa. In a few cases it was noted that at the lower levels of the cord the diffuse infiltration was marked and the perivascular changes not very severe, whereas at the upper levels of the same cord the perivascular infiltration was very severe while there

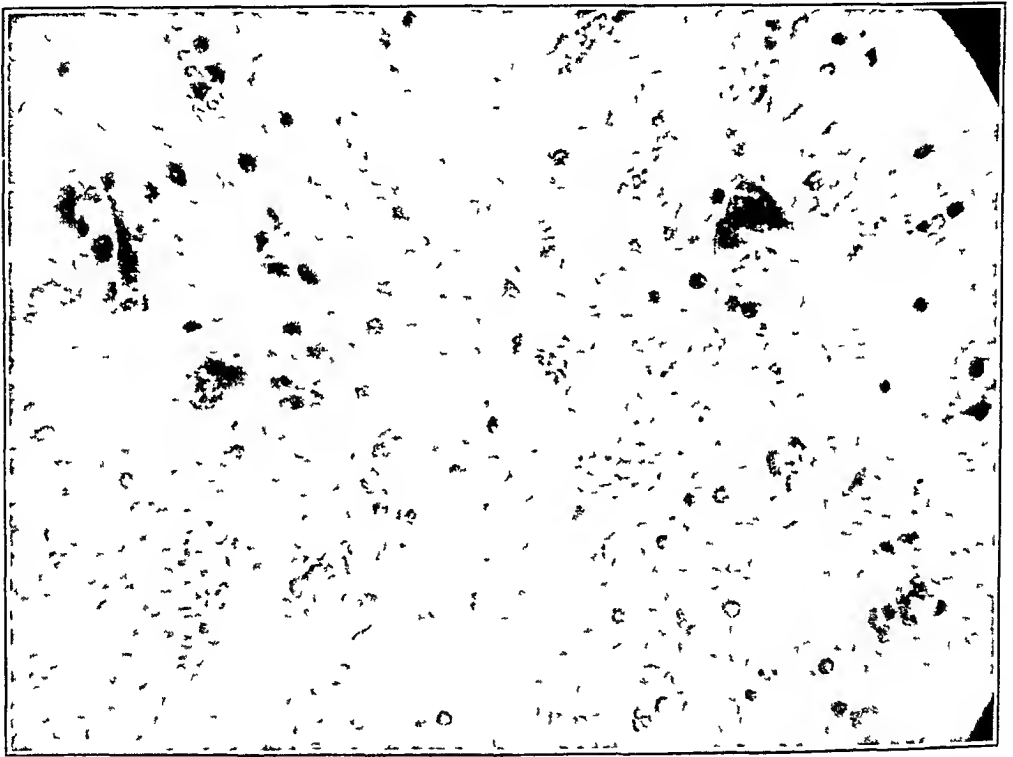


Fig 3—Section of cord showing considerable nerve cell degeneration with little or no cell infiltration

was little or no diffuse interstitial infiltration. This would indicate that the perivascular infiltration precedes the diffuse cellular infiltration and that the latter is derived from the former.

The cellular exudate consists largely of mononuclear cells, with a small sprinkling of polymorphonuclear cells. In two of the cases, the polymorphonuclears were the predominating cells. The mononuclears are of two varieties, one, with a round, deep blue, evenly stained nucleus with only a scanty amount of protoplasm around it, the other, with a nucleus which may be round or ovoid, pale staining, reticulated nucleus and a moderate amount of protoplasm around it. This is the polyblast as described by Maximov. It probably represents

the first type in an active state. The nuclei of the polyblast assume odd shapes such as the dumbbell, and the crescent. In some cells there is a division of the nuclear material forming the polyform cells described by Flexner as being present in the spinal fluid of monkey poliomyelitis. The first type of mononuclear cell predominates in the perivascular infiltrations whereas in the diffuse interstitial infiltrations the polyblast is the predominating cell type. This peculiar distribution can be readily explained by supposing that the cells in the perivascular infiltration are in the process of mobilization whereas those of the interstitial tissues are in the active process of destroying the virus and

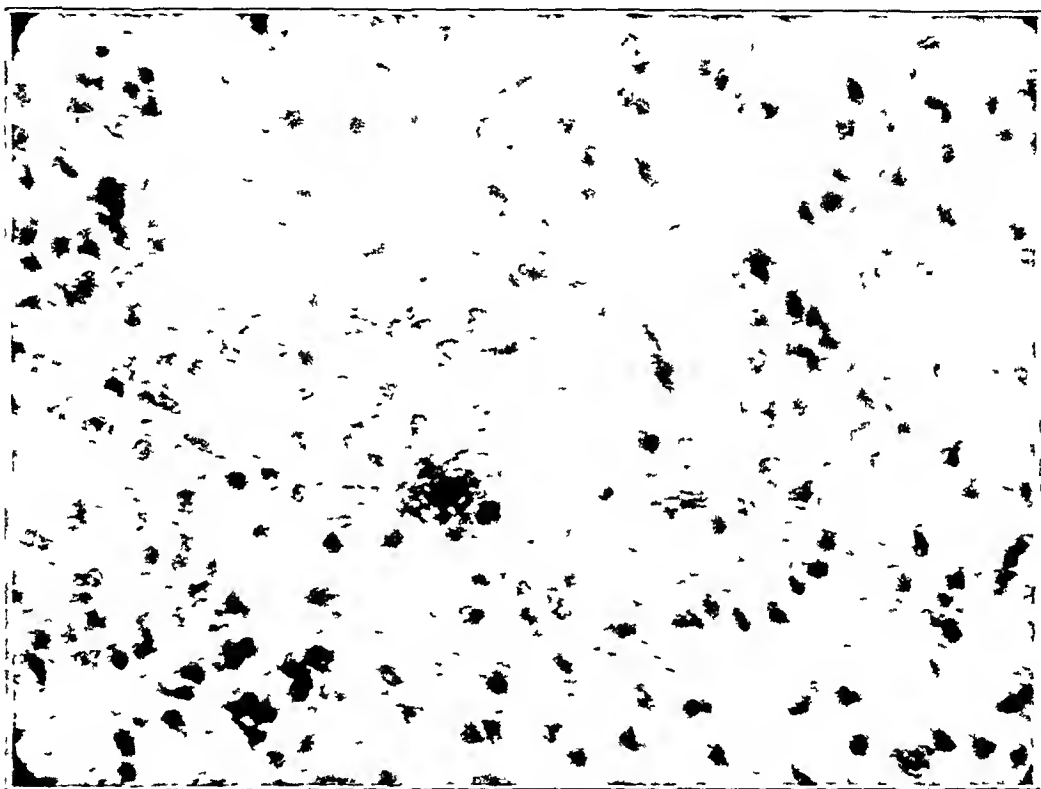


Fig. —Section of cord showing invasion of regenerated nerve cells by phagocytes

carrying off destroyed nerve cells. This would account for the change of the mononuclear into the polyblast. The source of these cells is undoubtedly the lymphatic system which discharges them into the central nervous system directly by the perivascular lymph spaces and indirectly by the blood stream. It is possible that the glia takes part in the acute infiltrative process but it is not very probable. Certainly the glia cells of the white matter show very little activity, and if they were responsive to the invasion of the virus, it is to be expected that they would proliferate more than is evident from study of the sections. There can be no doubt as to the part the glia plays in the process of repair, but they participate little if any in the acute infiltrative process.

Infiltration of the tissues with fluid was noted as being present in the gray matter in varying degrees and in not a few instances also in the white matter. The edema appears to make the tissue more spongy and separates the reticular meshwork. As Wickman has pointed out, the recession of edema may have much to do with the rapid disappearance of paralysis that is often observed in this disease.

Destructive effects on the nerve cells were noted in all the cases, those most commonly affected being in the anterior horns. Clarke's column suffered in those cases in which the posterior horns were markedly affected. In most cases, the intensity of the nerve cell



Fig 5—Pia from brain showing great thickening due to edema and cellular infiltration. Blood vessels are dilated and engorged.

destruction varied directly with the degree of interstitial cell infiltration. There were many sections, however, in which the nerve cell destruction was markedly out of proportion to the degree of cellular infiltration. A number presented extreme ganglion cell destruction with practically no interstitial change. On the other hand, there were cases with marked cellular infiltration in which the cells were in fair state of preservation. These are observations that corroborate the findings of Rissler and his followers.

The changes in the nerve cell progress from the loss of the Nissl's granules to complete hyalinization, in which all nuclear material is absent. In those cases in which the cell infiltration is marked, hardly a nerve cell is to be found. Here also are to be seen polyblasts

arranged in small groups in positions formerly occupied by nerve cells. This represents complete phagocytosis. Other degenerated nerve cells are to be seen in the process of being invaded by polyblasts. In those cases in which the cellular reaction is not marked and where considerable nerve cell damage exists, there are to be seen numbers of nerve cells in the state of hyaline degeneration. On the other hand, as already stated, where there is a marked cell reaction, there are few nerve cells to be seen. This is an observation which is pertinent to the question of the rôle performed by the interstitial elements in the pathology of this disease.

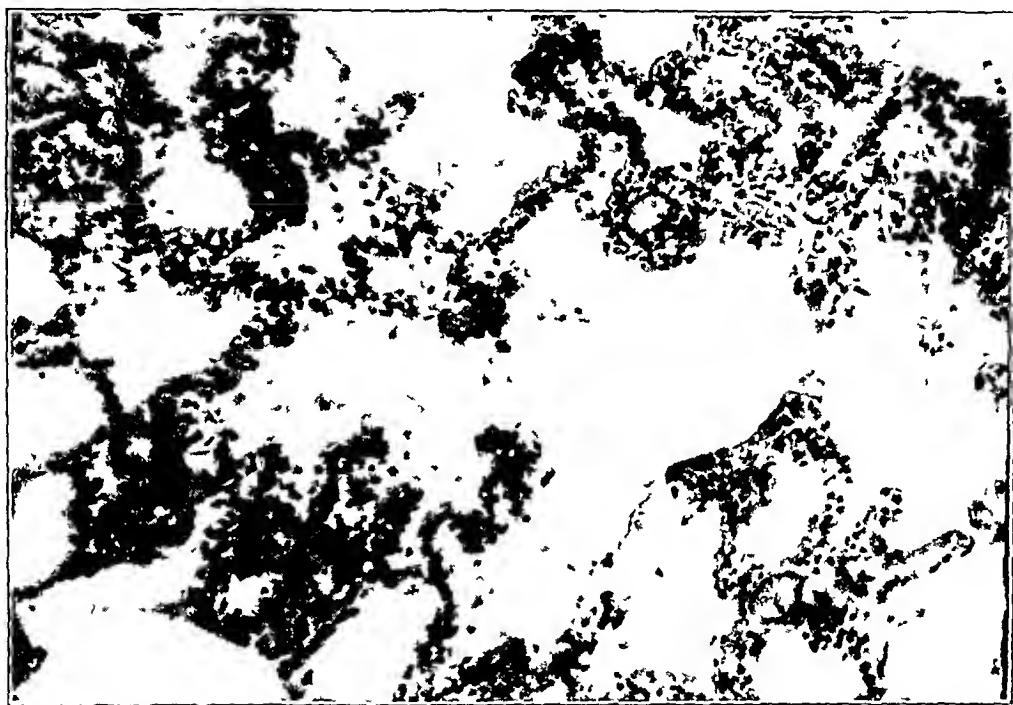


Fig 6—Section of lung showing thickened alveolar walls due to infiltration with small round cells

The pons and medulla exhibited round cell infiltrations and degenerative changes in thirty of the thirty-five cases examined. The remaining five showed marked congestion of the blood vessels. In one case, the pons and medulla presented the only changes found in the central nervous system. The cell infiltrations for the most part were located in between the bundles of fibers, with no tendency to localize in any particular region. Rarely were they found in the region of the nuclei. In nine of the cases there was marked diffuse infiltration. One section presented a large hemorrhage. The nerve cell changes were not as marked as in the cord. Often one group of nerve cells exhibited degenerative changes, whereas an immediately adjacent group would appear quite normal.

The changes in the cerebrum and cerebellum were very mild when compared with those in the cord. The most common change consisted of engorgement of the vessels, the endothelium of which had the appearance of being swollen. In fourteen of thirty-seven cases the brain exhibited very mild cell reactions, consisting in slight degree of perivascular infiltration and, in a few cases, in an accumulation of cells apart from the vessels. The nerve cells exhibited no degenerative changes. The cerebellum exhibited similar changes in five of thirty-three cases examined. These changes were most commonly found below cellular layers in the cerebrum and below the granular

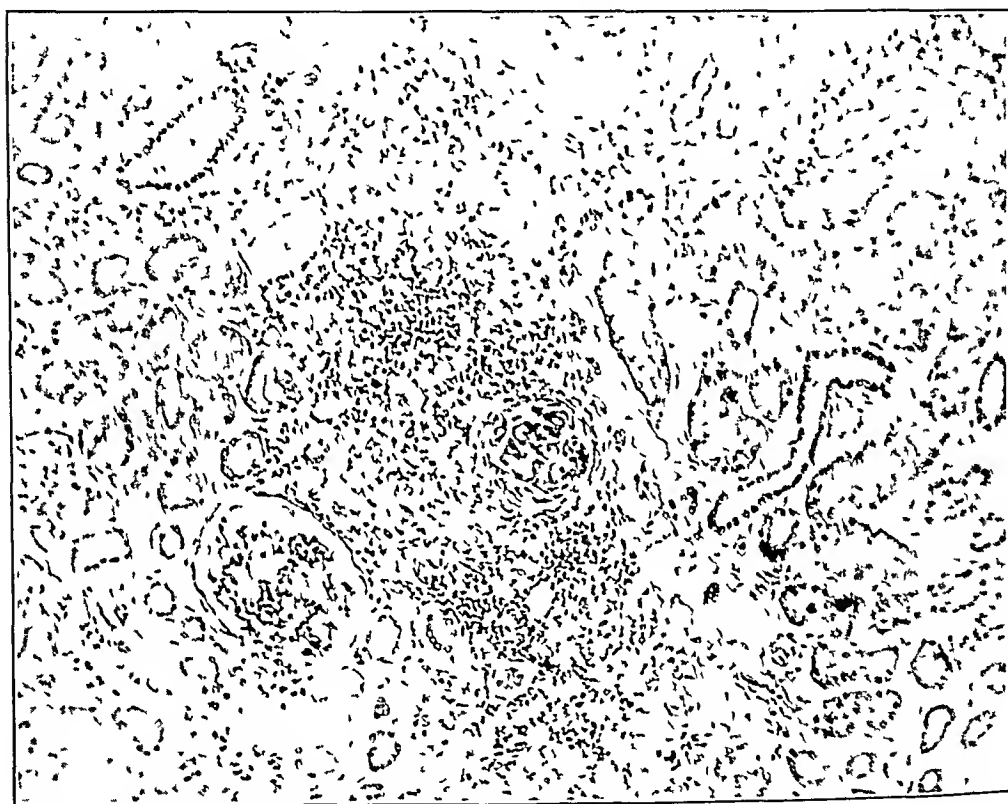


Fig 7—Section of kidney showing round cell infiltration and degeneration of glomeruli and tubules

and Purkinje cell layers in the cerebellum, in among the fibers radiating from the cortex. It is unfortunate that the sections of the two cortical cases have been lost, as they would undoubtedly have presented interesting changes.

CHANGES IN OTHER ORGANS

Careful studies were made of the lymphatic structures, particularly the agminated and solitary follicles of the small intestine, the mesenteric lymph nodes and the spleen. The thymus gland was studied in a few cases. Of twenty-nine cases in which the small intestine and mesenteric nodes were examined, sixteen presented distinct changes

In twenty-one of thirty-one cases the spleen presented similar changes. These consisted of a simple congestion of the blood vessels and distinct proliferation of the reticular cells, and marked hyperplasia of the endothelial cells. The germinating centers were increased in number and size and were very active. Moderate numbers of mitotic figures were present. The spleen in a number of instances presented intense congestion which dominated the picture. In no case was there attempt at ulceration of the intestinal mucosa over the lymphatic structures, and the adjacent mucosa failed to present cell infiltration such as one would expect in case of an active local inflammation, as in typhoid fever. In a number of cases, the lymphatic nodules adjacent to the bronchioles in the lungs exhibited changes as above described.

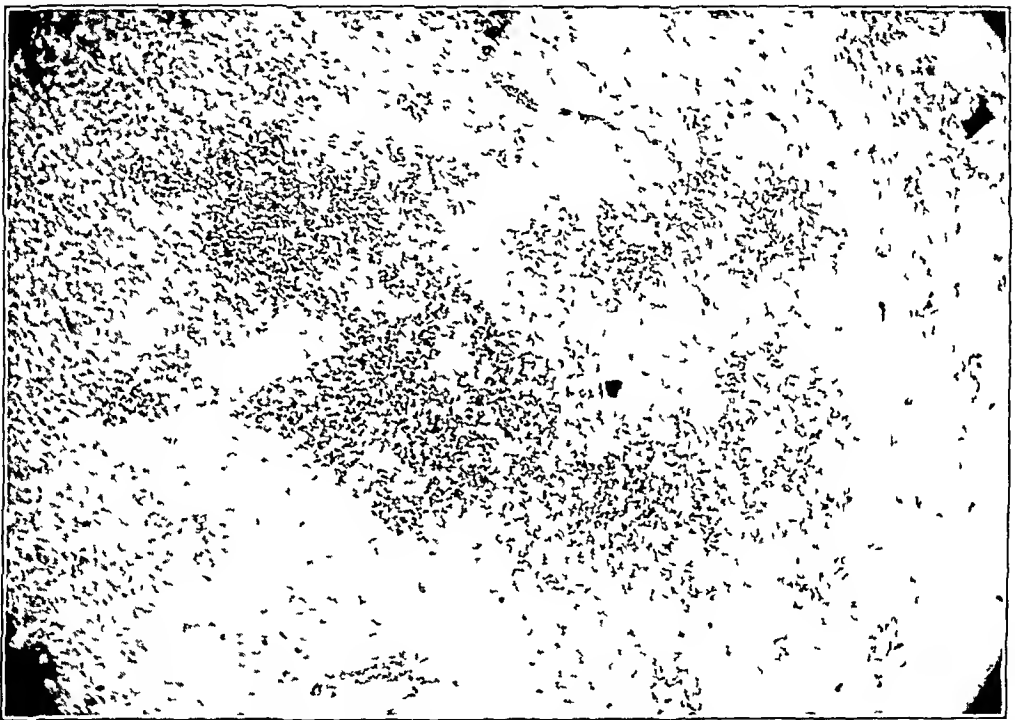


Fig 8—Large hemorrhage into cord

The lung capillaries were very often intensely engorged and tortuous. In a number of cases all vesicles presented an accumulation of fluid and desquamated epithelial cells. The majority of the lung sections examined presented a marked thickening of the alveolar walls, due in part to engorgement of the capillaries, but in the main to round cell infiltration. Some of the blood vessels presented a narrow collar of these cells very much like the perivascular changes observed in the cord proper. These changes may be the pathologic basis of the so-called "paralytic râles" observed by Louria.

The heart presented congestion of the small vessels, in many of which there was evidence of hyperplasia of the endothelial cells. In some instances there was slight perivascular arrangement of mono-

nuclear cells, such as Wickman had described in the subpericardial fat. These changes were noted only about thin walled vessels in the connective tissue septa between the muscle bundles. The larger, thick walled vessels did not exhibit such changes. The muscle fibers showed no pathologic change.

The liver, in quite a number of instances, exhibited an increase in small round cells in Glisson's capsule and some of the thin walled vessels presented endothelial hyperplasia. The entire vascular system was intensely engorged in many instances. Focal necroses such as described by Flexner, Peabody and Draper, were not noted, though

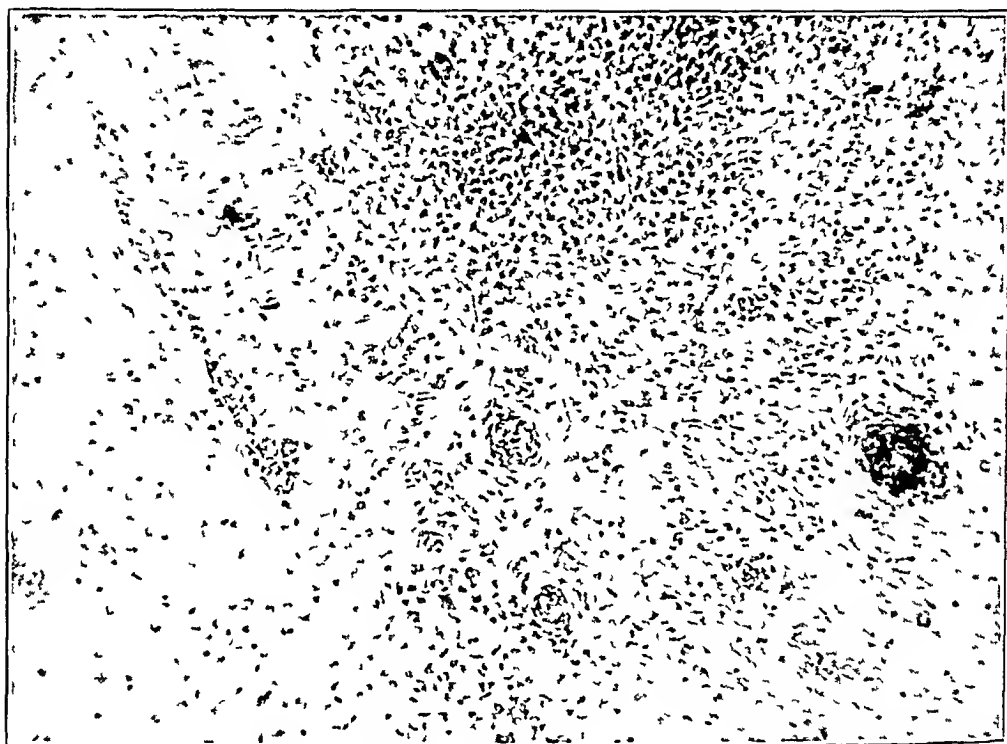


Fig 9—Section of cord. Marked diffuse infiltration, very slight perivascular cell infiltration.

in some cases there was marked hyaline degeneration of liver cells throughout a section and not localized in foci.

The kidneys in practically all instances were intensely engorged throughout both the cortex and medullary portion. In some cases there was to be seen hyperplasia of the endothelium of the malpighian tuft, so that it would appear as a ball of cells. These tufts appeared slightly smaller than adjacent tufts in which this hyperplasia was absent, perhaps due to the weight of the cells which prohibited the dilatation of the capillaries. Only occasionally was there evidence of parenchymatous degeneration. In two cases the kidneys presented focal accumulations of round cells, chiefly in the cortex. There was no evidence of a chronic inflammatory process such as one would

encounter in tuberculosis. The masses of round cells were disposed particularly around the glomeruli and produced degenerative changes in these, possibly by pressure. The cells infiltrated the spaces between the tubules, distorting relationship to each other and to the glomerulus. The tubular epithelium presented granular degeneration. Bowman's capsule was swollen and presented hyaline change. The capillaries were engorged. The changes presented all the characters of an acute process, except that the cell element was the mononuclear instead of the polynuclear. Whether these kidney changes are manifestations of the systemic disease is problematical. However, they are suggestive

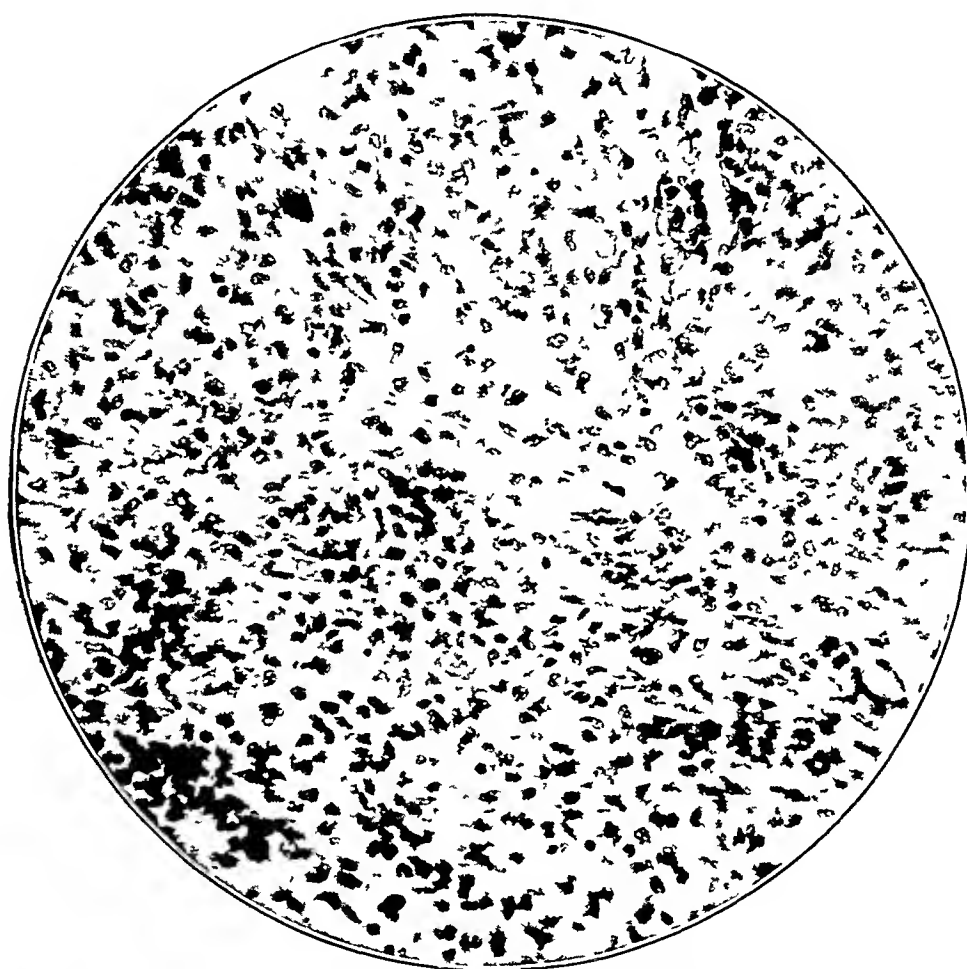


Fig 10—Section of cord showing intense diffuse cell infiltration but no perivascular infiltration

The pancreas and suprarenal capsule, aside from congestion and occasionally hyperplasia of the lymphatic elements, presented little that was abnormal.

The question arises, what is the significance of the changes observed in organs other than the central nervous system? The changes in the intestine are not such as to lead one to suspect it as being the portal of entry. The changes in the lymphatic system and endothelial hyperplasia observed in the other organs are undoubtedly a general response

of the body cells to an intense local infection situated in the central nervous system. Poliomyelitis is a local infection inasmuch as the chief anatomical lesions are situated in the central nervous system, but this local condition may engender a general response, just as in pneumonia the lung is the focus and the toxemia and the defensive response are general. The changes in the organs other than the central nervous system are not of a destructive character, but rather of a defensive nature.

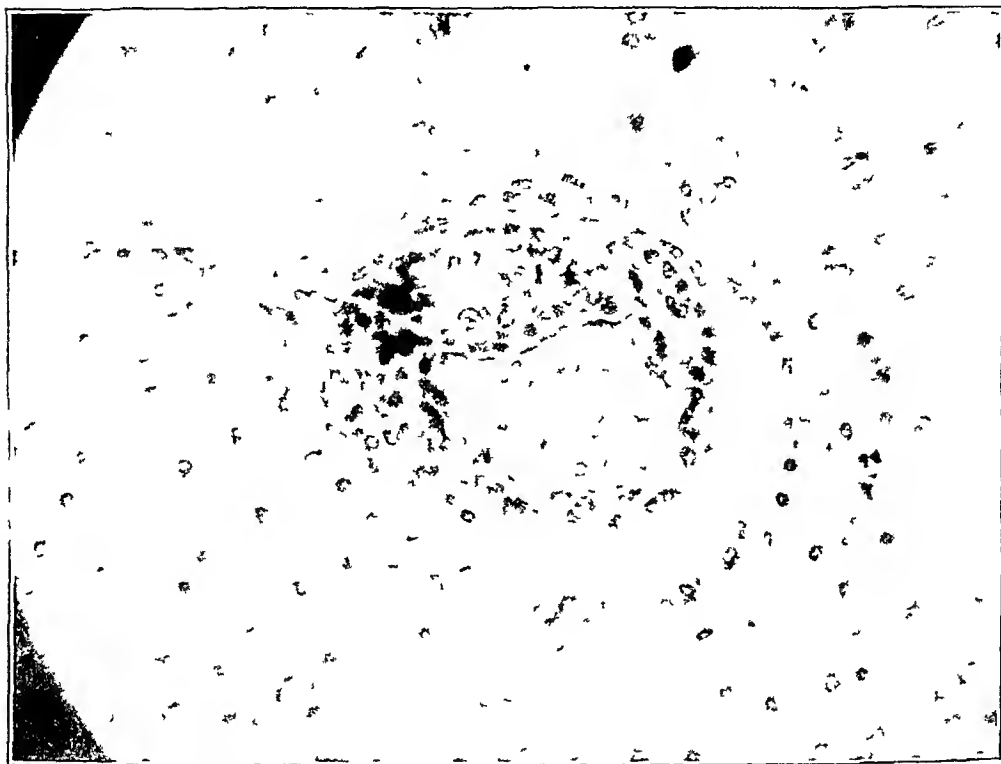


Fig 11—Section of cord. Perivascular cell infiltration, very little diffuse infiltration.

PATHOGENESIS

The question of pathogenesis has divided the workers in this field into two groups. One contends that the damage to the nerve cell is the primary lesion and the evidences of inflammatory changes are secondary, the other, that the inflammatory changes are the direct cause of the changes observed in the nerve cells. Charcot¹⁰ was the first to bring forth the first view. He was supported in this view by Rissler, who was the first to describe the pathologic changes in acute poliomyelitis.

Roger and Damaschino¹¹ were the first to advocate the primary importance of the interstitial changes. They have received strong

10 Charcot and Jaffray. *Arch. physiol. norm. et pathol.*, 1870.

11 Roger and Damaschino. *Rev. de med.*, 1881.

support from Wickman and Harbitz and Scheel, and a number of the more recent students of the disease. Wickman differs from Harbitz and Scheel in that he believes that the virus reaches the spinal cord by the way of the perineural lymphatics, whereas the latter authors contend that the path of infection is through the blood stream.

That the virus of poliomyelitis has a specific affinity for the nerve cells of the spinal cord, particularly those of the anterior horn, is indicated by the fact that no matter where the virus is introduced it reaches the spinal cord, whether by the subcutaneous, blood, intestinal, respiratory or intracerebral routes. The behavior of the virus in this respect is analogous to that of rabies. The bulk of experimental

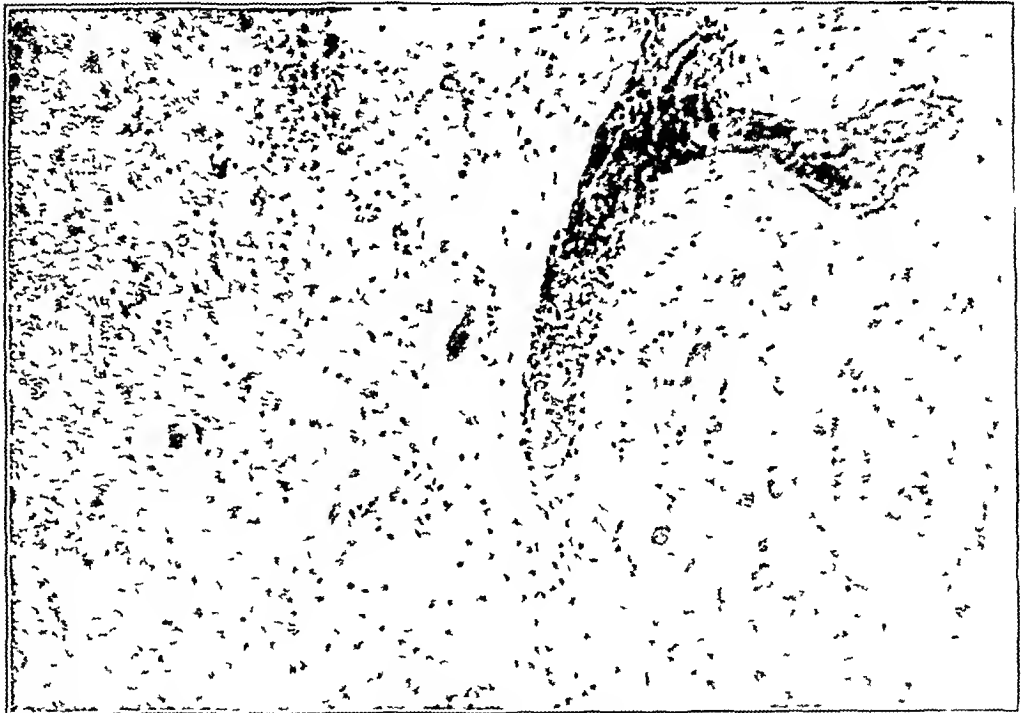


Fig 12—Section of cord. Marked perivascular cell infiltration, slight diffuse infiltration.

evidence thus far adduced strongly indicates that the virus reaches the central nervous system by way of the perineural lymph channels. It has been proved that the rabic virus takes a similar path to reach the central nervous system. The majority of the workers concede that the perineural lymph route is without a doubt the path of infection. Harbitz and Scheel, however, contend that the virus reaches the pia from the blood and spreads from this site to the cord itself along the sheaths of the blood vessels. Experimental work, however, has not supported this idea.

It would appear that Wickman's ideas of the pathogenesis are somewhat inconsistent. To grant that the virus reaches the cord by

the perineural lymph channels, that the lymph which bathes the nerve cell contains the virus of poliomyelitis, and yet to consider that the nerve cell destruction is brought about by the interstitial phenomena is at variance with what is logical in such circumstances. Furthermore, Rissler, Cassierer and also the present study, present evidence which would indicate that the marked nerve cell destruction can exist with a minimum of inflammatory reaction. Kling, Petterson and Wernstedt¹² have observed changes in monkey poliomyelitis which they described as purely degenerative in character. Because interstitial changes occur in the great majority of cases along with nerve cell changes is no reason for the assumption that the former produces the latter. The fact that there is evidence, even though small in quantity, that nerve cell destruction may be present with a minimum of cell reaction is sufficient to overbalance the fact that nerve cell destruction is so prevalent in sections showing marked cellular infiltrations. To assume that polyblasts have the power of invading healthy and intact nerve cells and destroying them, is rather far fetched. A more logical assumption would be that the nerve cells being destroyed or damaged are fit subjects for the phagocytic activities of the polyblasts. This, too would explain why in those sections that present marked cell destruction there is a marked accumulation of polyblasts. Furthermore, it would explain why apparently healthy and intact nerve cells are present in the midst of a densely infiltrated zone without the sign of being subjected to phagocytosis. Those cases in which the interstitial change is so slight though there is considerable evidence of nerve cell destruction, can be explained by diminished ability to react to the virus which primarily affects the nerve cells.

The pathogenesis of acute poliomyelitis, in the opinion of the writer is as follows:

The virus has a special affinity for nerve cells, more particularly the anterior horn cells. It reaches the central nervous system by way of the perineural lymph channels. The process spreads in the central nervous system by the lymphatics. The congestion, edema and cellular infiltration, whether present in the pia or in the cord itself, are the cardinal elements of an inflammatory reaction in response to injury produced by the activity of the virus in the cord. The neurophagocytosis is not an active primary destructive process, but rather the exercise of the known normal functions of leukocytes that of carrying off destroyed material. The congestion and edema, undoubtedly, play a considerable part in the production of transient paralysis through pressure effects.

¹² Kling, Petterson and Wernstedt *Ztschr f Immunitätsf*, **12**, 316 and 657, **14**, 303, 1912 **16**, 17

FURTHER OBSERVATIONS ON THE ABERRANT ELECTROCARDIOGRAM ASSOCIATED WITH SCLEROSIS OF THE ATRIOVENTRICULAR BUNDLE BRANCHES AND THEIR TERMINAL ARBORIZATIONS

CLINICAL AND HISTOLOGIC REPORT OF A CASE IN WHICH SUCH ABERRANT COMPLEXES WERE OBTAINED*

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In a previous paper¹ we reported the clinical observations on twenty-two cases in which *aberrant* electrocardiograms were obtained, attributing the abnormal type of the ventricular complex to a temporary or permanent defect in conductivity of the branches of the atrioventricular bundle

As characterizing the essential difference between the *aberrant* electrocardiogram and the normal type, we emphasized the prolongation of the P-R interval beyond 0.20 second, the increase in the duration of the QRS interval beyond 0.10 second, particularly when it constitutes more than one third of the duration of the entire complex; the deflection of the T-wave in a direction opposite to that of the prominent initial deflections, with frequent conspicuous exaggeration of its amplitude, the relatively increased amplitude of the initial deflections of the ventricular complex in an opposite direction in Leads I and III, often markedly notched, and finally, the tendency of these deflections to assume a diphasic rather than a triphasic or quadriphasic type

In this earlier report, based wholly on material collected in Dr Lewis' laboratory in London, no attempt was made to discuss the nature of the histologic changes in any of the cases of this series that came to necropsy. The evidence for our conclusions as to the nature of the defect in conductivity was apparently well established by the *then* available experimental work of Eppinger and Rothberger² by the observations of Eppinger and Stoerk³ who had in two cases, con-

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* From the Medical Clinic of the Cleveland City Hospital and the Western Reserve University

1 THE ARCHIVES INT MED, 1914, **13**, 803

2 Eppinger and Rothberger Ztschr f klin Med, 1910, **70**, 1

3 Eppinger and Stoerk Ztschr f klin Med, 1910, **71**, 157

firmed by a histologic examination the clinical diagnosis, made from the electrocardiogram, of a lesion of the right branch of the atrio-ventricular bundle, and by the case reported by Cohn and Lewis⁴ of atrial fibrillation and heart block, in which the histologic examination showed a destruction of both branches of the atrioventricular bundle, the electrocardiograms obtained from this case being practically identical with the curves obtained from a *similar experimental* lesion by Eppinger and Rothberger

In a previous report of four cases characterized by abnormal electrocardiograms, Mathewson⁵ asserted that "in the present state of our

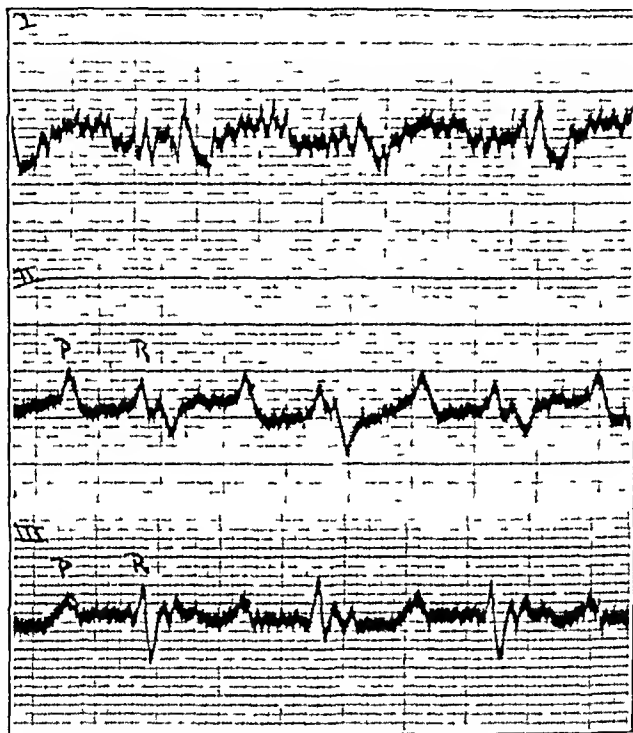


Fig 1—March 21, 1916 The P-R interval measures 0.24 second The QRS measures 0.16 second The T-wave is inconspicuous, especially in Lead II It is upright in Lead I and inverted in Lead III The QRS complex shows more than a simple notching, having a distinct triphasic character It cannot be said that the conspicuous initial ventricular deflections are in a direction opposite to each other in Leads I and III Their voltage as expressed by amplitude is low This record taken on admission to the hospital *before* digitalis was given

In this and the succeeding figures 1 scale of divisions of ordinates equals 10^{-4} volts, 1 scale of the abscissae equals 0.04 second

knowledge, the alterations in the electrocardiographic curves may be regarded as indicating interference with the normal stimulus conduction in the branches of the bundle"

4 Cohn and Lewis Heart, 1912, 4, 15

5 Mathewson Heart, 1913, 4, 385

Since the publication of our earlier series we have learned⁶ that four of the hearts included in this report did not show, on histologic study of the material available, any evidence of definite lesions of either branch of the atrioventricular bundle

In a recent paper Oppenheimer and Rothschild⁷ report a study of sixty-two cases characterized by abnormal electrocardiograms, together with the results of a detailed histologic study of eleven of the hearts obtained from the fourteen necropsies in the twenty-five known fatal cases of their series. Thirteen of these hearts showed a widely disseminated patchy sclerosis of the myocardium, predominating in the endocardial and subendocardial layers, these changes being grossly

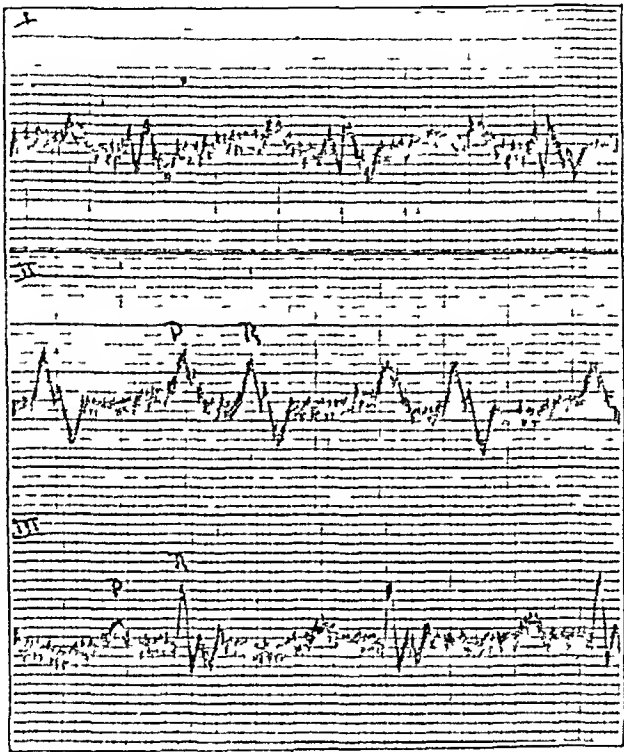


Fig 2—May 10, 1916. The P-R interval measures 0.24 second. The QRS interval measures 0.16 second. The T-wave is still inconspicuous. In Lead I the P-wave is to be made out. The conspicuous initial ventricular deflections are triphasic in Leads I and III, and of relatively low amplitude. In Lead II the notch comes on the descent of R almost at the iso-electric level. In Lead III R is conspicuous with a notched peak and is followed by a curiously split complex. After digitalis.

more marked in the left than in the right ventricle. Eight hearts showed also coronary artery sclerosis with occlusion of the anterior descending branch of the left coronary, while four showed nodular sclerosis of the coronary arteries with no occlusion.

⁶ Personal communication.

⁷ Oppenheimer and Rothschild. Jour Am Med Assn, 1917, 69, 429.

These observers further emphasize as the criteria for determining the abnormal electrocardiogram the prolongation of the QRS complex beyond 0.10 second, the notching of R, and call attention to the low voltage, as expressed by the low amplitude of the deflections in all three leads and the absence of the typical diphasic curves with large T'-waves seen in experimental bundle lesions. Referring to the earlier series of cases reported by the writer they say that they regard most of them as cases similar to those they describe, and call attention to the existing discrepancy between previous electrocardiographic interpretation and the pathologic findings.

In the light of our present knowledge of the occurrence of widely scattered foci of sclerosis involving chiefly the terminal fibers of the

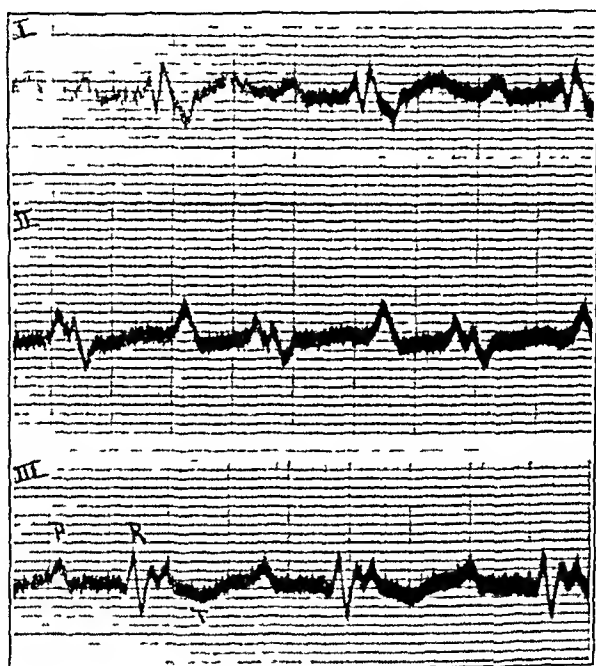


Fig 3—Oct 29, 1916 On readmission. The P-R interval measures 0.26 second. The QRS interval measures 0.16 second. The T-wave is slightly more conspicuous and in a direction opposite to the conspicuous initial ventricular deflections. The QRS complex shows the same bizarre type of triphasic character, this being especially marked in Leads I and III. Before digitalis.

conduction system and giving rise to a conspicuously altered QRS complex, it is apparent that we must revise our clinical interpretation of the aberrant electrocardiogram.

In a study of a fairly large series of cases throughout the past two years we have been impressed by the frequent occurrence of aberrant electrocardiograms characterized by curves of low amplitude in all three leads and an absence of the large diphasic curves so closely simulating the experimental bundle lesion. In some instances we have been astonished by the occurrence of curves of low amplitude alternat-

ing with curves of high amplitude in the same individual, occasionally seen at but short intervals of time. We have also been impressed by the frequent occurrence of prolongation of the QRS complex with bizarre notching, and the constancy of the opposite direction of the initial deflections in Leads I and III, in the absence of any increase in the P-R interval, and by the observation that the QRS complex, although prolonged, does not in many instances, at least, attain a duration of one-third of the entire ventricular complex.

The final deflection T' appears however, remarkably constant in its direction opposite to that of the conspicuous initial deflections in

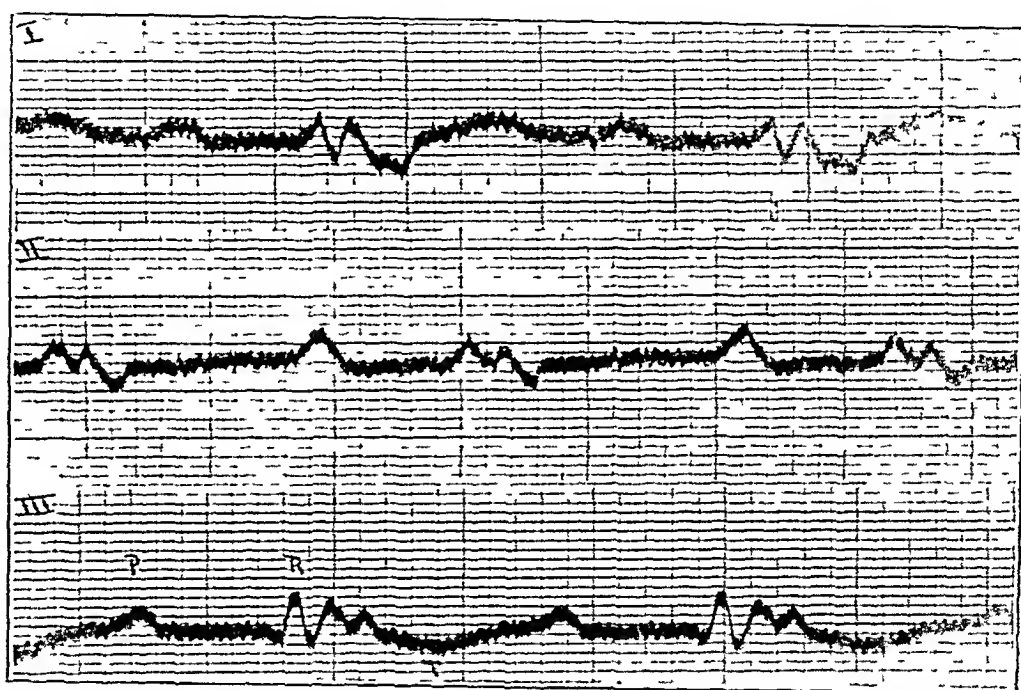


Fig 4—Oct 29, 1916 In order to bring out the essential features of the electrocardiogram this record was taken with the plate dropping at a speed of 68 cm per second. The low amplitude and the bizarre type of the ventricular complex are plainly seen in all three leads. Before digitalis.

Leads I and III, being inverted in Lead I and upright in Lead III, with the single exception of case 299 in our series. In case 248, cited later, this inversion is, of course, reversed during the paroxysmal attack, appearing in a direction opposite to that of the conspicuous initial deflections both during the presence of the *normal* and the *abnormal* mechanism.

What is most interesting is the fact that we have seen but a single instance simulating the experimental curves of a left bundle lesion, such as illustrated Case 13 of our earlier series and this only during an attack of paroxysmal tachycardia (Case 248, Fig 7).

These points are clearly shown in the accompanying Table, in which we have grouped in tabular form thirteen cases showing conspicuous aberrant electrocardiograms taken from the last 108 of our serial cases

There are but two cases of this series which merit any detailed discussion. The chief points of the aberrant electrocardiogram that we wish to emphasize and which are brought out by the case reported herewith in detail, and not included in this table, are seen at a glance

TABLE 1—CASES SHOWING CONSPICUOUS ABERRANT ELECTROCARDIOGRAMS

Serial No	Duration of P-R Interval*	Duration of QRS Complex	Duration of Total Ventricular Complex	Notching of R and S	Direction of Initial Deflections in Leads I and III	Direction of T in Relation to Initial Deflections in Leads I and III	Voltage as Expressed by Amplitude of Ordinate $\times 10^{-4}$
217		0 10	0 18	Notched	Opposite	Opposite	Low
237		0 10	0 32	Notched	Opposite	Opposite	Low
255		0 10	0 30	Notched	Opposite	Opposite	Low
248 During tachycardia		0 16	0 20	Notched	Opposite	Opposite	Very high
With normal mechanism	0 19	0 07	0 32	None	Opposite	Opposite	Normal
279	0 17	0 12	0 36	Notched	Opposite	Opposite	High
282		0 08	0 28	Notched	Opposite	Opposite	Low
286		0 09	0 32	Notched	Opposite	Opposite	Low
294		0 11	0 28	Notched	Opposite	Opposite	Normal
299	0 19	0 11	0 32	Notched	Opposite	Same	Low
306	0 19	0 10	0 36	Notched	Opposite	Opposite	Low
311		0 08	0 34	Notched	Opposite	Opposite	Low
324		0 11	0 36	Notched	Same	Opposite	Low
325a		0 14	0 48	Notched	Opposite	Opposite	Very high
325b		0 12	0 48	Notched	Opposite	Opposite	Low

* The P-R interval is given in those instances only in which it measured at least 0.17 second or more

Case 248 was remarkable in that during the attack of paroxysmal tachycardia the general type of the electrocardiogram was so conspicuously altered. During the normal mechanism the conspicuous initial deflections were in opposite directions, being upright in Lead I and inverted in Lead III, and the final deflection T appeared in an opposite direction in both leads. In Lead II the ventricular complex appears normal, lacking wholly any evidence of its bizarre character which appeared during the paroxysm. The P-R interval is increased, measuring 0.19 second. The inversion of the P-wave in Lead III, Figure 6, we are at a loss to account for. It is not altogether easy to

assume that this is an expression of a change of focus for the pacemaker in this lead, when in the presence of a definitely altered focus we get the anomalous complex noted below

We have noted a similar inversion of the P-wave in a number of instances, both in the normal individual and in pathologic cases, quite constantly occurring in Lead III, and not accompanied by any conspicuous shortening of the P-R interval Lewis, Meakins and White⁸

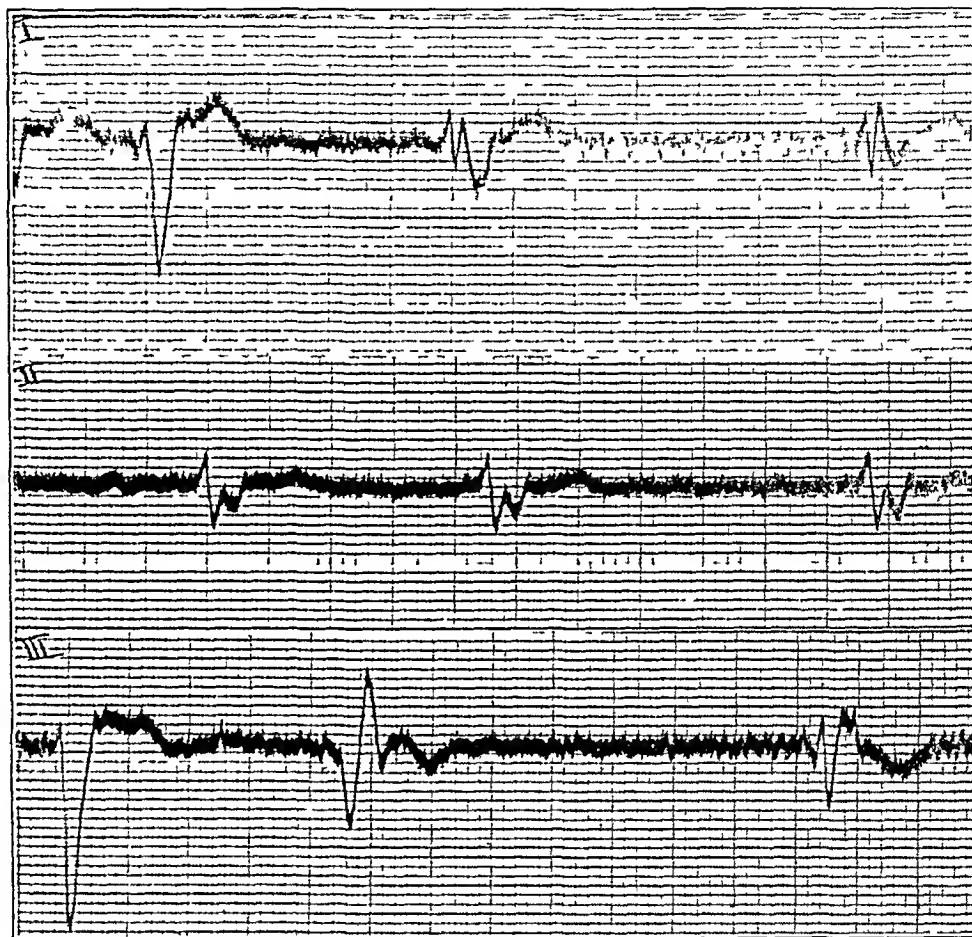


Fig 5—Feb 3, 1917 After the onset of atrial fibrillation The anomalous ventricular complex is more marked The normal ventricular sequence is disturbed by premature beats arising from the left ventricle and junctional (?) tissue Note the slightly increased amplitude of the initial ventricular deflections in this figure The T-wave has increased in amplitude above the previous figures and can be distinctly made out There has been, however, no reversal of its negativity Digitalis was given to the point of marked slowing with digitalis coupling

in their experimental observations on the excitatory process in the dog's heart, have recorded a shifting of the pacemaker *within* the S-A node as a result of vagal stimulation with such inversion

⁸ Lewis, Meakins and White Phil Tr Roy Soc, London, Series B, 1914, 205, 375

Wilson,⁹ in a paper calling attention to changes in the location of the cardiac pacemaker associated with respiration, has divided these changes into three classes (1) migration of the pacemaker within the sinus node, or within its immediate neighborhood, (2) migration of the pacemaker from the sinus node to the a-v node, and (3) escape of the idioventricular rhythm with complete atrioventricular dissociation, during which the ventricles contracted more rapidly than the auricles

In a recent very interesting paper on heart block, Wilson and Robinson¹⁰ in describing similar changes in the P-wave advance the view that these alterations are analogous to the change which may occur in the experimental animal under vagal stimulation

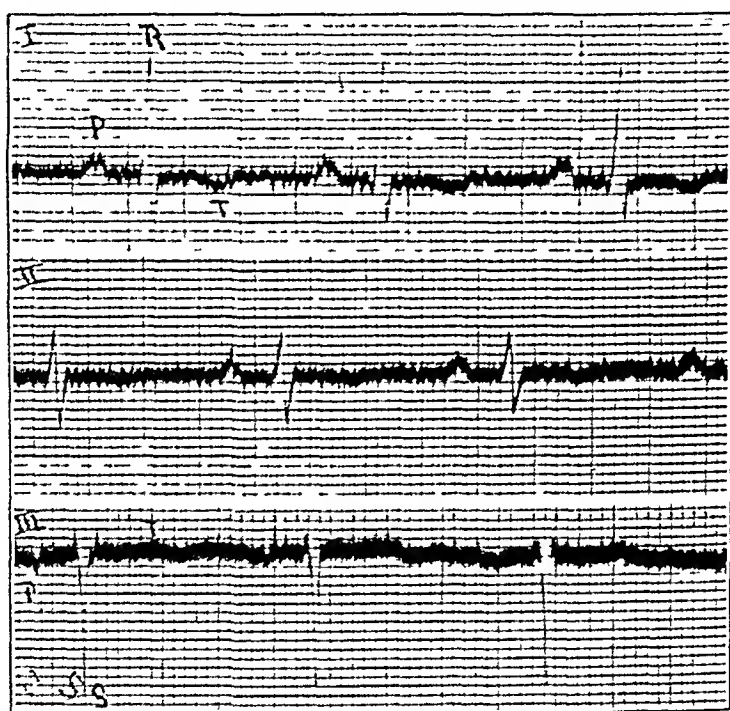


Fig 6 — Same case as Figure 7 During the presence of the normal mechanism There is absolutely no suggestion of the abnormal complex seen during the tachycardia In Lead III the P-wave is inverted

In our own observations we have been able to classify this inversion of the P-wave, seen so constantly in Lead III, into essentially two groups one in which it is definitely under vagus control and becomes upright under atropin, and one in which vagus control is apparently in abeyance, neither atropin nor vagus stimulation having any effect on the inversion

During the paroxysmal tachycardia in this instance the whole type of the ventricular complex was altered, being characterized by curves

9 Wilson, F N THE ARCHIVES INT MED, 1915, 16, 86

10 Wilson and Robinson THE ARCHIVES INT MED, 1918, 21, 166

of high amplitude essentially diphasic, which fact considered alone is not, of course, unusual, but when considered in the light of the direction of the conspicuous initial deflections, with the suggested notching of R' and S' in Leads I and III, the conspicuously altered complex in Lead II, and the great increase in the QRS complex is significant (Fig 7)

These curves, obtained during the tachycardia, represent the single instance which has come under our observation in which the electro-

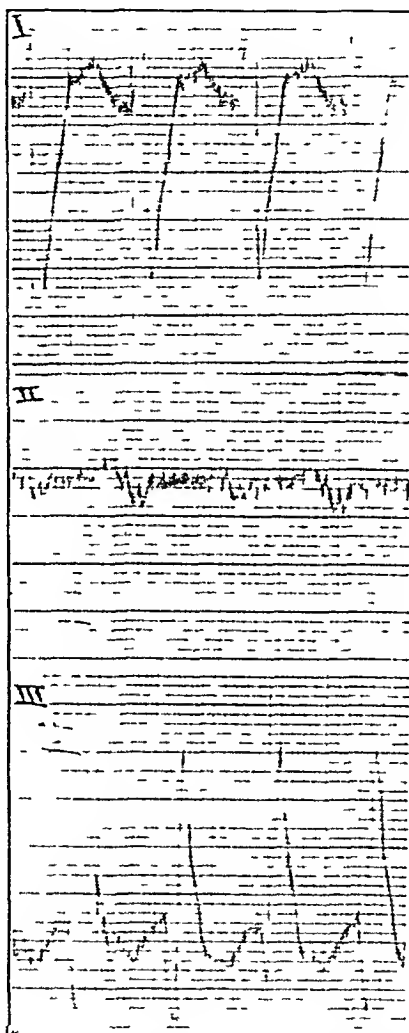


Fig 7—Illustrating Case 248 during the attack of paroxysmal tachycardia. Note the direction of the conspicuous initial deflections, with notching, in Leads I and III, and the anomalous complex in Lead II. Ventricular rate 180

cardiogram showed diphasic curves of large amplitude with a conspicuous S' in Lead I and R' in Lead III, and a marked prolongation of the QRS complex, in so far simulating the curves obtained from experimental lesion of the *left* branch of the atrioventricular bundle

As illustrating the occurrence of curves of high amplitude alternating with those of low amplitude, Case 325 is a striking example

In this case the electrocardiogram obtained on admission showed, in the presence of a complete atrioventricular dissociation, typically diphasic curves of large amplitude, remarkably similar to the published experimental curves of Eppinger and Rotchberger following section of the right atrioventricular bundle branch in the dog (Fig 8) Twenty-four hours later the large diphasic curves had disappeared and given place to an entirely different type of ventricular complex characterized

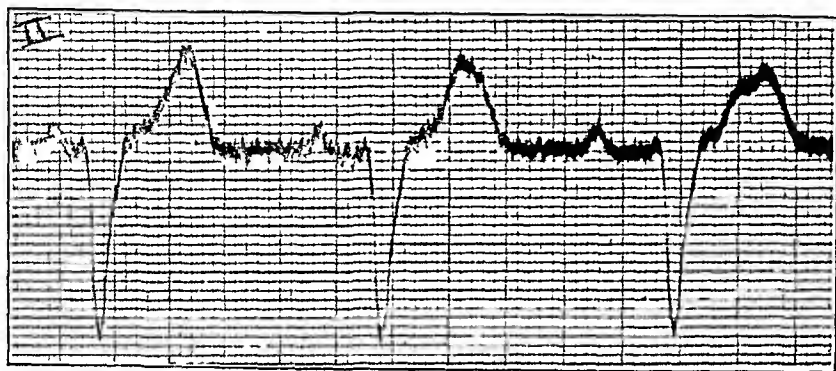


Fig 8—Illustrating Case 325 Record taken on admission to the hospital Complete A-V dissociation Lead II Note the greatly increased amplitude of the ventricular complex and its diphasic character S' shows suggestive notching The QRS interval measures 0.12 second

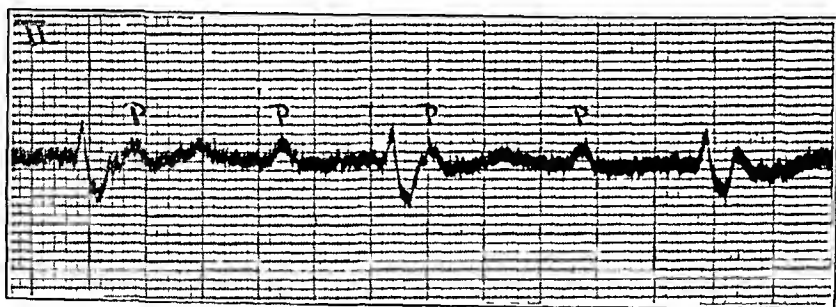


Fig 9—Illustrating Case 325 Twenty-four hours after Figure 8 had been taken Lead II Note the low amplitude of the ventricular complex with marked notching of S' The QRS interval measures 0.12 second

by curves of low voltage, as expressed by amplitude, with a slightly shorter QRS complex (Fig 9)

How shall we interpret such widely divergent types of curves obtained in so short an interval of time? In the earlier curves the initial deflections have a value expressed in microvolts of 3,200 (32×10^4), while later their value is but 900 micro volts (9×10^4) Are we justified in assuming that the earlier records were obtained at a time when there existed a definite but temporary failure of con-

duction in the right bundle branch, which altered the *assumed* dominant type of the electrocardiogram as shown by the later curves? Based on the experimental evidence available, no other interpretation seems quite logical

In the thirteen cases tabulated we have expressed the range of voltage, as illustrated by the amplitude of the initial deflections, as low, normal, high and very high, assuming that the so-called "normal" taken by itself is but an average standard, subject to considerable variation, but that in the presence of advanced myocardial disease the values "low" and "high" have a definite pathologic significance

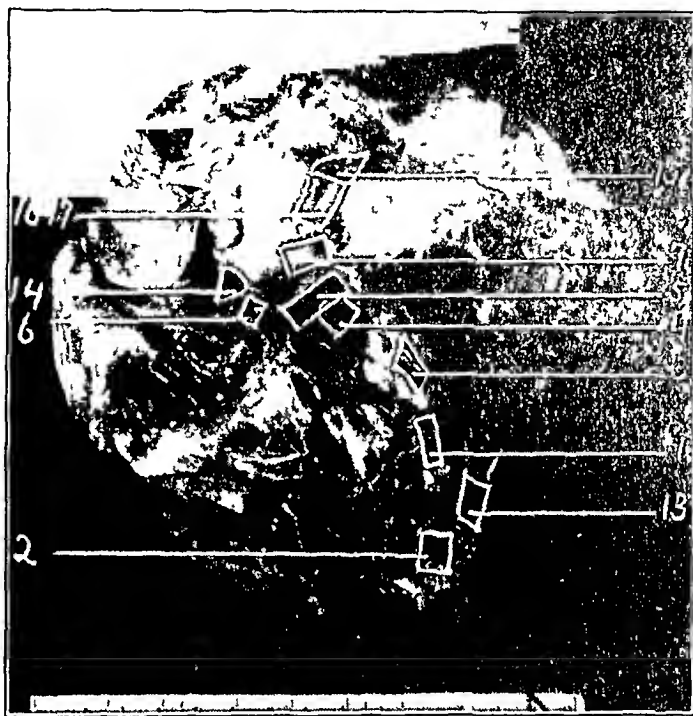


Fig 10—Right side of heart opened to show right atrium and ventricle, and areas of tissue blocks removed

It will be seen that out of these thirteen cases, with the exception of Case 248, which showed a typically *aberrant* electrocardiogram only during the paroxysm of tachycardia, and Case 325, in which the earlier curves simulated the experimental bundle lesion, but one, Case 279, fulfilled the essential requirements for the diagnosis of a definite bundle branch lesion, being characterized by curves of large amplitude typically diphasic. All the other cases conform essentially to the type of curve illustrating the case we are reporting in detail, though lacking the conspicuous triphasic character of the ventricular complex so constant a feature of this case

It will be further noted that three of the cases included in this

table did not show an increase in the duration of the QRS complex beyond 0.10 second. In so far as the prolongation of this complex constitutes a vital criterion for determining the presence of marked sclerosis throughout the conduction system, these cases should possibly be excluded. On the other hand, the electrocardiographic records obtained from these cases were in every other respect so typical of the general type under discussion that we have included them.

DETAILED REPORT OF CASE

It is greatly to be regretted that in many instances in our series we have been unable to secure a necropsy. In the case the subject of this

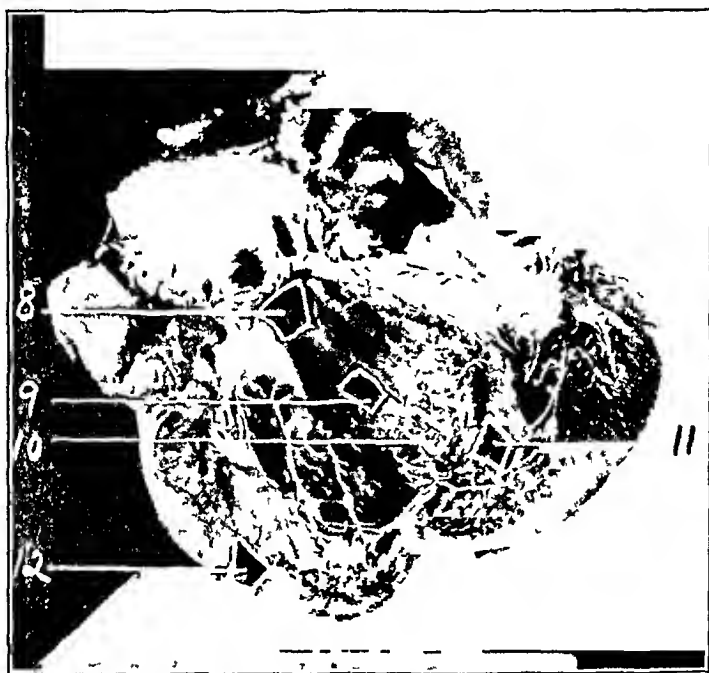


Fig. 11—Left side of heart opened to show areas of tissue blocks removed

note the heart was removed immediately after death and taken at once to Professor Van der Stricht¹¹ to whom we are indebted for the histologic study and report.

Clinical History—Clinical Diagnosis—Syphilitic myocarditis and aortitis, cardiac hypertrophy, atrial fibrillation, chronic nephritis and emphysema, cardiac failure and death.

The patient, S. S., a laborer, aged 42, was admitted to the City Hospital, Jan. 1, 1915, complaining of cough, shortness of breath on exertion and swelling of the feet. The family history was negative.

¹¹ The writer wishes to express his great indebtedness to Prof. O. Van der Stricht of the University of Ghent, now at the Johns Hopkins University, for his elaborate and detailed study of the heart from this case.

Personal History—Typhoid fever at 24, pneumonia at 25. The patient says that in 1910 he had "rheumatism" in his right leg. No history could be obtained of acute rheumatic fever, and no history of any joint involvement associated with this so-called "rheumatism." He was not confined to bed at this time. He admits the history of a venereal lesion in 1900. He had had a specific urethritis several times. Used alcohol to excess up to 1912. Had had four breakdowns similar to the present attack, characterized by shortness of breath on exertion and some swelling of the feet, the first in 1910, the last in 1914.

Present Illness—The present acute onset of symptoms dated from Jan. 1, 1915, when following a sudden overexertion lifting heavy baggage he became short of breath on the slightest exertion. This distress in breathing was soon followed by swelling of his feet and legs. He walked into the hospital.



Fig. 12—Transverse section through the left posterior ventricular branch of the bundle in the septal wall (Piece 9). Magnification 85 diameters. Showing infiltration and the extreme degree of fibrosis present in and around the bundle.

Condition on Admission—The patient was a well developed and well nourished colored man. He was very dyspneic and coughed a good deal. The head showed no exostoses or protuberances. The ears were negative. There was no mastoid tenderness. The pupils were equal, reacted very sluggishly to light, but readily to accommodation. There was no nystagmus, strabismus or ptosis. The teeth were very poor, many badly carious molars, pyorrhea was present, tongue coated.

There was no enlargement or tenderness of the palpable lymphatic glands.

There were no deformities of the spine or long bones, and no thickening of the periosteum or of any of the joints.

Thorax This was well formed, anteroposterior diameter increased, subcostal angle margins flared equally on inspiration, no prominence of supraclavicular fossae. The percussion note was resonant throughout, but slightly higher pitched over the right apex posteriorly. The breath sounds were everywhere vesicular in character, expiration being prolonged. At both bases

posteriorly and in the left scapular region medium moist râles were heard at the end of inspiration and beginning of expiration. Tactile fremitus was present throughout, with normal variations.

Heart There was well marked precordial activity over a wide area. The point of maximum impulse was in the sixth interspace 16.5 cm from the midsternal line, apex impulse forcible, diastolic impact palpable over the base in the third interspace, no thrills or reduplications palpable. The upper border of cardiac dullness was in the second interspace extending 8 cm to the left and 3 cm to the right, in the third interspace dullness extended 13.5 cm to the left and 3.5 to the right, in the fourth interspace, 15 cm to the left and 5 cm to the right, in the fifth interspace 15.5 cm to the left and 8 cm to the right, and in the sixth interspace 16 cm to the left, and to the right was merged in hepatic flatness. These measurements are from the midsternal line. No murmurs or friction rubs were heard. The first sound at the apex had a booming quality, the second sound at the base was accentuated, with a slightly tympanic quality.



Fig 13—Transverse section through the left posterior ventricular branch of the bundle in the septal wall (Piece 9). Magnification 535 diameters. Showing the conspicuous cleavage of the Purkinje fibers.

The pulse rate was 96 to the minute, regular, of equal volume and synchronous in both radials. The systolic pressure was 120, diastolic 90.

Liver and spleen were not palpable.

Abdomen No free fluid, abdominal muscles of good tone, no general or localized tenderness.

There was edema of both legs and ankles and complete right inguinal hernia.

Reflexes Biceps and triceps reflexes equal and active, patellar and Achilles reflexes could not be elicited, normal plantar reflex.

Urine The specific gravity varied from 1.010 to 1.018, albumin from a trace to an excessive amount was constantly present, microscopically, hyaline and granular casts were present.

The temperature remained practically normal throughout the period of observation. The Wassermann reaction was strongly positive.

The patient remained in the hospital at this time about four months, making only a fair recovery, but was able to undergo a successful surgical operation for the inguinal hernia, and was discharged June 26, 1915. No electrocardiographic records were obtained at this time as our galvanometer was not yet installed.

Readmitted March 21, 1916, with marked symptoms of failure of cardiac reserve. Extreme dyspnea, edema of legs and free fluid in the abdomen.

Heart. Marked precordial activity over a wide area, upper border of cardiac dulness at second interspace, point of maximum impulse in fourth interspace 17 cm. from midsternal line, left border of cardiac dulness 18 cm. from midsternal line in sixth interspace, right border 5.5 cm. from midsternal line in fifth interspace, sounds distant, at apex first sound was booming in character, second sound was sharply accentuated, the second pulmonic being louder than the second aortic, no murmurs could be made out, pulse rapid, regular, of moderate volume, tension increased.



Fig. 14—Transverse section of the right atrioventricular junction, A-V node (Piece 5). Magnification 45 diameters. Showing the extraordinary degree of fibrosis of the main stem of the bundle.

At this time the patient was under observation until June 23, 1916, when he left the hospital at his own request in fair condition. The first electrocardiographic records were obtained during this period. (See discussion of figures.)

Readmitted again Oct. 23, 1916. He said that he had only been able to do the slightest work since his discharge. Ten days previously the shortness of breath and swelling of the feet became so severe that he was compelled to seek hospital care.

His condition at this time was one of great discomfort, owing to the extreme dyspnea and edema. His extremities were so swollen that he walked with great difficulty. The liver was greatly enlarged and there was free fluid in the abdomen.

Course in the Hospital—From this time until his death he remained under observation. He showed still a certain power of response to rest and treatment, but his heart was unable to recover to anything like the extent noted on previous admissions.

The cardiac dulness was as already noted, with a marked increase in the area of dulness to the left and to the right over the aortic area. At this time a soft systolic murmur was noted at the apex on admission, but disappeared, to return again later, though never pronounced. It was regarded as a relative mitral insufficiency.

His cardiac mechanism remained normal up to Dec 15, 1916, when atrial fibrillation developed. His blood pressure remained at or about 120 to 130 systolic and 80 to 90 diastolic up to the onset of fibrillation. The urine contained albumin in excess and many hyaline and granular casts. Death ensued Feb 10, 1917.

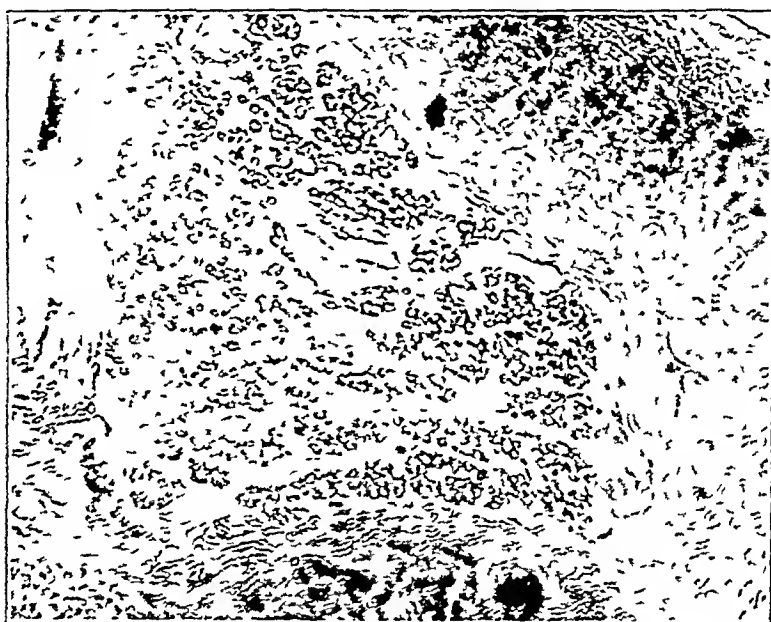


Fig 15—Transverse section of the stem of the bundle under the endocardium of the right ventricle beneath the septal cusp of the tricuspid valve (Piece 4). Magnification 103 diameters. Showing the great amount of fibrosis and cicatrization present.

DISCUSSION OF ELECTROCARDIOGRAMS

In selecting the figures for reproduction in this report we have chosen from a large series a number of records taken at fairly wide intervals of time, which represent the dominant type of electrocardiogram obtained throughout the period of observation, and illustrate clearly the abnormal ventricular complex so striking a feature of this case.

Voltage of Cardiogram as Expressed by Amplitude—The high voltage as expressed by the amplitude of the P-wave, and the low voltage of the ventricular complex are at once apparent. Up to the time of the onset of atrial fibrillation the average value of the P-wave

expressed in microvolts remained practically constant in all three leads. 400 microvolts in Lead II and from 100 to 200 in Leads I and III respectively. The amplitude of the ventricular complex, though never marked showed a gradual increase towards the end, particularly in Leads I and III. In Lead II it ranged from 600 microvolts (Fig. 4) to 1000 microvolts (Fig. 2). In Leads I and III the amplitude of the ventricular complex was constantly as great as, or greater than, that seen in Lead II, attaining in Figure 5 a value of 1700 microvolts.

More interesting is the low value of the T-wave seen early and its slight though distinct increase in the later stages following digitalis when it reached a value of 300 microvolts. Although showing an increase in amplitude at no time was there any reversal of its negativity.

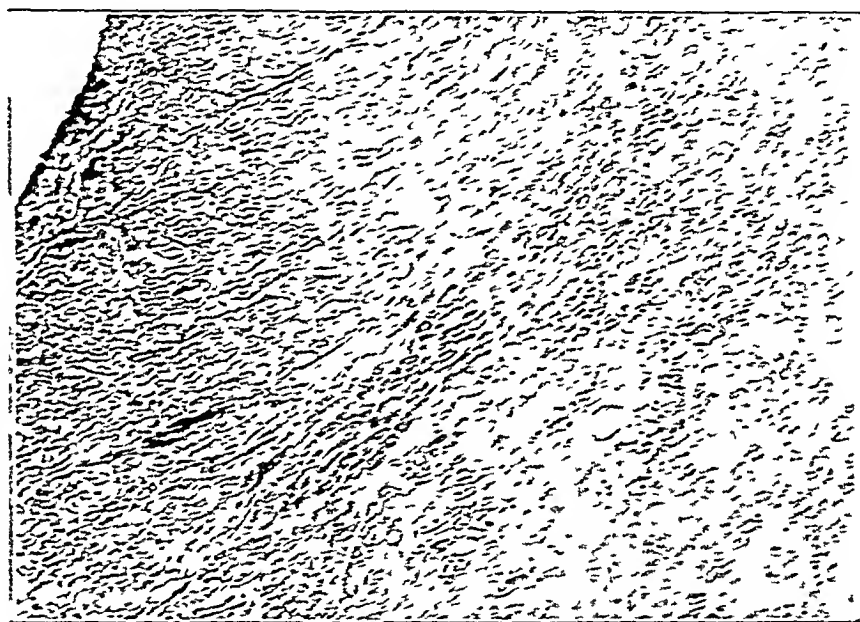


Fig. 16—Section of the wall of the right atrium from block of tissue taken immediately above and including the margin of the coronary sinus (Piece 5). Magnification 103 diameters. To show the fibrosis of the atrial wall. The Purkinje fibers appear larger and are stained lighter than the cardiac fibers.

The QRS Complex—The type of the QRS deflections of the ventricular complex remained constant throughout, only tending to increase the distinctness of their triphasic character as the disease progressed. The duration of the QRS interval remained constant at 0.16 second, with the exception of the measurement in Lead II (Fig. 4), where it is but 0.14 second.

The conspicuous notching of this complex seen as an interruption in the return to the iso-electric line in Figures 1 and 2 appears as a distinct alteration in negativity in Figures 3 and 4 especially marked in the latter figure, in which the plate moved at a greater speed. So

distinct was this evidence that we were inclined to assume that there might be a definite sequence in the contraction of the right and left ventricles. Keeping this possibility in mind we sought constantly for a reduplication or doubling of the first sound of the heart, hoping to obtain at least some clinical evidence of an asynchronous systole, but with negative results, as no such doubling was noted. We must not forget, however, that the electrical complex represents the propagation of the excitation wave, a change in electrical potentiality, and not a muscular action.

The T-Wave—The amplitude of the T-wave, never marked, increased distinctly, attaining a value of 300 microvolts (Fig 5, Leads I and III). These negatives were taken after a prolonged course of digitalis, which, however, did not alter the P-R interval, nor the direction of the T-wave. In Lead II this wave remained practically isoelectric.

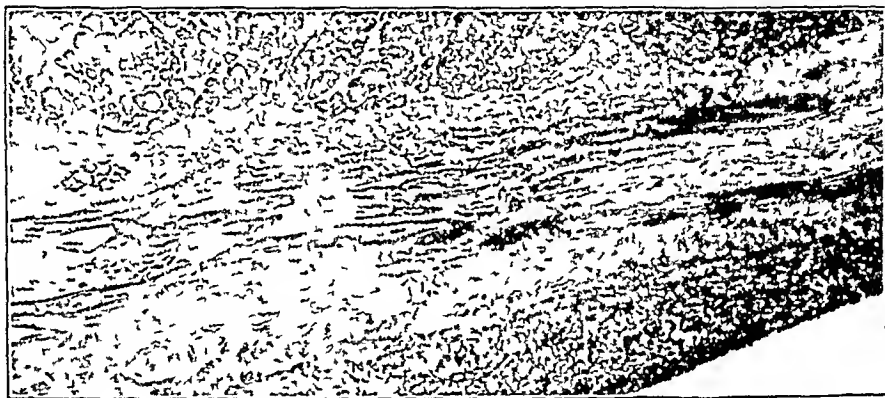


Fig 17—Longitudinal section of the left posterior branch of the atrio-ventricular bundle just below the right coronary cusp of the aortic valve. At this site the bundle first appears under the endocardium of the left ventricle (Piece 8). Magnification 103 diameters. The extent of the fibrosis in and around the bundle is plainly evident.

The failure to obtain any increase in the P-R interval or alteration in the negativity of the T-wave is in line with our results in a number of observations which it is hoped to make the subject of a future report. Using a standardized preparation, we have found, as have other observers, a striking dissimilarity in the response to the drug.

Relation of the Electrocardiogram to the Cardiac Hypertrophy—In the light of our knowledge of the relationship of the electrocardiogram to the predominance of hypertrophy of one or the other ventricles, as shown by Lewis¹² and by Cotton,¹³ our curves gave no clue to the preponderating muscle mass present in this case in the left ven-

12 Lewis Heart, 1914, 5, 367

13 Cotton Heart, 1917, 6, 217

ticle It is, to be sure, true that we were dealing with a heart clinically greatly enlarged in all directions, but the striking post-mortem feature was the great increase in the mass of the left ventricle as compared with the right, which was essentially dilated It is perhaps justifiable to assume that the normal course of the current of action was so interfered with by the diffuse sclerosis present throughout the conduction system, especially in the left ventricle, that the usual electrical complex so typical of a conspicuous unilateral ventricular hypertrophy was annulled

PATHOLOGIC REPORT

Heart The heart is greatly enlarged, weight, 770 gm The length from the root of the pulmonary artery to the apex is 125 mm The amount of fat is not increased There are large "milk spots" on both ventricles The pericardium is normal The right and left atria are large and their walls thick,



Fig 18—Transverse section of the base of the posterior papillary muscle of the left ventricle at its point of union with the trabecula containing the left posterior branch of the bundle (Piece 11) The extreme degree of fibrosis in and around the bundle is clearly shown

but neither shows the marked enlargement and hypertrophy apparent in the ventricles The right wall of the right atrium at the lower end of the crista terminalis measures 5 mm in thickness, that of the left atrium immediately above the orifices of the pulmonary valves is also 5 mm thick The actual muscular wall of the right ventricle (not including any of the prominent trabeculae carneae) between the papillary muscles is 6.5 mm in thickness, and the diameter of the wall of the left ventricle in a corresponding situation measures 16 mm Near the atrioventricular junction the cross section of the right ventricular wall is 7 mm and that of the left ventricle 20 mm There is no apparent endocarditis The cusps of all four valves are free and normal The right atrioventricular orifice admits four fingers, into the left the entire

five can be passed as far as the proximal interphalangeal joint. The orifices of both coronary arteries are surrounded by atheromatous patches, and there is a diffuse sclerosis of both vessels throughout, possibly more marked in the left than in the right branch. Neither coronary is occluded. There is a marked patchy sclerosis of the beginning of the aorta. There is marked enlargement of the ventricular trabeculae and papillary muscles.

On opening the right side a well marked *pars membranacea septi* is to be observed, in the lower margin of which the bundle can be fairly well seen. Immediately in front of the fibrous septum there is marked cicatrization along the course of the bundle which can be identified under the endocardium right into the moderator band and so to the anterior papillary muscle. In the right atrium, strands of Purkinje fibers are visible on the septal wall, passing from the upper part of the crista toward the atrioventricular junction. Similar bands terminating in the same location can be seen running from the region of the coronary orifice. Blocks of tissue about 10 mm square and 5 mm thick were cut from the several areas recorded later. In removing such blocks of tissue it is sometimes difficult to be sure that the Purkinje fibers have been included, especially if they lie deeply in the myocardium. If the cut edge of the block be examined promptly, however, the retraction of the Purkinje bundles, always greater than that of the myocardial fibers in the perfectly fresh organ, brings about a localized dimpling of the cut surface which immediately sets all doubts at rest. In this heart we were particularly fortunate in observing the dimpling in every piece removed except numbers 4 and 5, where much cicatrization occurred.

On opening the left ventricle the bundles show less definitely. The anterior and middle limbs immediately disappear among the unusually marked trabeculae and no attempt was made to secure these. The posterior branch is plainly visible in its course toward the posterior papillary muscle and portions of it were obtained as stated later. No histologic examination was made of the left atrium.

The branches of the coronary vessels in the atrioventricular junction and those passing along the main branches of the Purkinje system are not obvious to the naked eye.

After the tissue blocks had been removed the heart was photographed and then preserved by Kaiserling's method.

The following is the list of the sites from which the tissue blocks were removed.

Right Ventricle and Atrium

Piece 1 Moderator band (*trabecula supraventricularis*) near base of papillary muscle.

Piece 2 Anterior papillary muscle at site of entrance of moderator band.

Piece 3 Right branch of bundle on septal wall proximal to moderator band.

Piece 4 Stem of bundle under the endocardium of the right ventricle beneath septal cusp of tricuspid valve. This portion includes the commencement of the right and left main branches. It is greatly cicatrized (Fig 15).

Piece 5 *Pars membranacea septi* immediately above and behind Piece 4, but, unlike the latter, which is from the interventricular part of the septum, this is from the septum between the right atrium and the left ventricle (Fig 14).

Piece 6 Tissue of the coronary groove of the right atrium immediately above and including the margin of the orifice of the coronary sinus (Fig 16).

Piece 7 Part of the septal wall of the right atrium immediately above and adjacent to the noncoronary cusp of the aortic valve. (We follow Keith's nomenclature in reference to the aortic cusps.)

Piece 13 Piece of ventral wall of the right ventricle for myocardial fibers.

Piece 14 Interatrial septum between coronary orifice and fossa ovalis, including the margin of the latter. This block is from the wall above and behind Piece 6.

Piece 15 Block from right atrial wall adjoining the orifice of the superior vena cava and including the upper extremity of the crista terminalis and the muscular ring at the junction between the atrial canal and atrial appendix. From this block Pieces 16 and 17 were sliced off.

Left Ventricle

Piece 8 Left branch of the atrioventricular bundle immediately below the right coronary cusp of the aortic valve before the bundle has broken up into its three left constituent limbs. This block contains the bundle where it first appears under the endocardium of the left ventricle (Fig. 17).

Piece 9 Left posterior branch of the bundle in the septal wall. This was the only branch visible to the naked eye in the left ventricle (Figs. 12 and 13).

Piece 10 Continuation of left posterior branch passing among the trabecular tissue between septal wall and the posterior papillary muscle.

Piece 11 Base of the posterior papillary muscle at its point of union with the trabecula containing the left posterior branch of the bundle (Fig. 18).

Piece 12 Block from the ventricular wall at the base of the anterior papillary muscle for myocardial fibers.

Figures 10 and 11 illustrate graphically the great increase in thickness of the left ventricular wall as compared with the right, and also show the exact positions from which the various tissue blocks were removed.

TABLE 2—EXTENT OF PATHOLOGIC ALTERATION PRESENT IN THE HEART

Piece No	Fibrosis in the Atrioventricular Bundle	Piece No	Fibrosis in the Atrioventricular Bundle
1	Diffuse	9	Well marked
2	Diffuse	10	Well marked
3	None	11	Well marked
5	Slight	12	Slight
6	Slight	15	Slight
7	None	16	None
8	Diffuse		

We shall not discuss the methods of procedure followed in the detailed study of this heart but shall summarize briefly Professor Van der Stricht's observations on the pathologic alterations present in so far as they are of interest in connection with the clinical report and the electrocardiographic analysis. For a detailed study the reader should consult Professor Van der Stricht's monograph to appear elsewhere.

Table 2 shows the extent of pathologic alteration present in the various pieces as enumerated in the foregoing.

It will thus be seen that with the exception of Pieces 3, 7 and 16 there is evidence of more or less marked inflammatory invasion of the bundle tract throughout, being particularly conspicuous in Pieces 9, 10 and 11 from the left posterior branch below its division, and "diffuse" in this branch just before dividing into its three constituent left limb. This inflammatory reaction is characterized by a round cell infiltration and a sclerosis of the interstitial connective tissue associated with a "cleavage" process affecting the individual Parkinje cells, many of which undergo an exaggerated cleavage more or less pathologic

and others again divide and subdivide until they are reduced to the condition of atrophic cells in process of complete disappearance" (Figs 12 and 13)

In addition to this localized inflammation affecting the left posterior branch of the bundle, the majority of the segments, as already noted, show a diffuse inflammatory reaction of the bundle tract and its superficial endocardium, involving particularly in the left ventricle the terminal arborizations of the Purkinje network

It is interesting to note further that there was a conspicuous sclerosis and atrophy of the tunica media, both of the larger arteries and of the smaller arterial branches in the atrioventricular bundle in the majority of the segments described, lesions which must have affected seriously the nutrition of the cells concerned. The coronary arteries were simply sclerosed throughout but not occluded

It is then evident that in addition to sclerotic lesions involving in localized exaggerated foci the main stem of the atrioventricular bundle at the point of the right and left main branches (Fig 15, Piece 4), and the left posterior branch of the bundle (Figs 12 and 13, Piece 9), there existed throughout the entire bundle tract a most extraordinary diffuse sclerotic process profoundly affecting the entire conduction system

SUMMARY

It is apparent that in the extent of the diffuse sclerosis present involving the terminal arborizations of the Purkinje system, this case corresponds closely to the series reported by Oppenheimer and Rothschild,⁷ but that in the degree to which localized areas of fibrosis and cicatrization were present in the main stem and the left posterior branch of the bundle differs from the cases described by these observers (Figs 12, 13 and 14), conforming in the first instance, both histologically and in the electrocardiographic records, to the type designated by them under the general term "intraventricular block" as "arborization block," and in the second instance, histologically only, to the type designated as bundle branch block

We have hitherto accepted the large diphasic curves of greatly increased amplitude as conclusive evidence of a definite bundle branch lesion of such magnitude as seriously to interrupt the normal course of the excitation wave. In the presence of the extraordinary amount of fibrosis and cicatrization seen in the main stem and the left posterior branch of the bundle in this heart, it is difficult to believe that there was not serious interference with the normal conduction of the excitation wave in this part of the bundle tract, and yet at no time were large diphasic curves recorded. In spite of these demonstrable focal lesions, curves of relatively low voltage were invariably present

Referring to Table 1, it will be seen that expressed in terms of amplitude, the majority of the cases cited gave curves of low voltage, so characteristic of the complex recorded in this case, and considered as indicative of a diffuse sclerosis throughout the terminal fibers of the Purkinje system. That, however, in the presence of low voltage curves of the type designated we are justified in assuming more than a predominance of such a distribution of the sclerosis and can always exclude definite localized lesions of the main stem and its branches would seem, in the light of the evidence of this heart, to be untenable.

It is further apparent that many cases showing distinct electrocardiographic evidence of bundle lesions and fibrosis of the terminal arborizations may not show any increase in the P-R interval, and in some instances, depending no doubt on the extent of the fibrosis, no, or but slight, increase in the duration of the QRS complex.

Electrocardiographic curves of low amplitude, with slight or greatly prolonged QRS interval, associated with notched initial ventricular deflections, in opposite directions in Leads I and III, and with the T-wave in a direction opposite to these initial peaks, represent essentially the ventricular complex seen in the presence of a predominant diffuse sclerosis involving chiefly the terminal arborizations, but are also compatible with associated localized focal lesions of the main stem and branches of the atrioventricular bundle.

CONCLUSIONS

- 1 The presence of a predominant diffuse sclerosis of the terminal arborizations of the Purkinje system gives rise to electrocardiographic curves of low amplitude, associated with a bizarre ventricular complex of a definite type.

- 2 Curves of large amplitude, essentially diphasic, may justly be regarded, from the experimental evidence available, as indicative of a definite totally obstructive, temporary or permanent lesion of one of the branches of the atrioventricular bundle.

- 3 The presence of curves of low amplitude, so characteristic of a diffuse sclerosis, did not, however, preclude the existence of definitely localized focal lesions involving the main stem and its branches.

2275 Tudor Drive

THE EPIDEMIC OF MUMPS AT CAMP WHEELER, OCTOBER, 1917-MARCH, 1918*

LIEUT M J RADIN, M R C
CAMP WHEELER, GA

It is through the kindness and courtesy of Maj Joseph Sailer, M R C, Chief of Medical Service at the Base Hospital, Camp Wheeler, Georgia, that this paper is presented. Methods of procedure, arrangement of the work and inspiration for a rather monotonous task were all drawn from him by the various ward surgeons who have treated mumps. It is due to him alone — and this cannot be too clearly stated — that a stupid and insignificant disease became interesting.

Patients with mumps have occupied almost half of the hospital for three months. An epidemic of such volume raises mumps to the dignity of a disease. Of approximately 18,000 men in the Thirty-First Division, there were 5,756 cases, an incidence of 32 per cent. Every third man in the division, in other words, has had mumps. Of 13,638 total admissions to the hospital to March, 1918, almost one half were mumps — to be exact, 42.2 per cent. Sporadic cases occurred from October 17, 1917, when the first patient was admitted, to November 20, when the epidemic started with 18 admissions. The next increase was on December 3, an interval of two weeks, on which day there were 46 admissions. The third increase occurred December 14, ten days later, when there were 86 admissions. The fourth rise was on December 27, with 133 admissions, and the final increase to the apex of the epidemic was on January 15, on which day there were 140 admissions. The total admissions on this day — all diseases — was 194. There were 624 cases of mumps in the hospital at one time, December 30. Corresponding falls occurred in the admission rate.

It is regrettable that such a slight, and, in a measure, preventable, disease has occupied so much time, energy and material. Lieutenant Hathcock estimates that the cost of the epidemic to the government was at least \$1,000,000.

Mumps is defined by Osler as "a specific infectious disease, characterized by swelling of the salivary glands and a special liability to orchitis in males." It might be added that it is self-limited and its complications temporary and functional.

ANATOMY

Anatomic considerations should have brief mention. The parotid gland weighs from $\frac{1}{2}$ to 2 ounces. It lies below and in front of the external ear, limited above by the zygoma and below by the angle of

* Submitted for publication June 6, 1918

the mastoid and a line drawn horizontally from this point to the mastoid process. The external carotid artery is buried in it and the facial nerve crosses it transversely. Stenson's duct is $2\frac{1}{2}$ inches long and opens into the mouth opposite the second upper molar. The blood supply is from the external carotid. Nerves issue from the carotid plexus of the sympathetic, fascial, and branches of auriculotemporal and great auricular.

Submaxillary Gland—This gland weighs about 8 drams. It is placed under the lower jaw, lying on the mylohyoid, stylohyoid and hyoglossus muscles. It is separated from the parotid by the stylo-mandibular ligament. The facial artery is imbedded in a groove on the posterior surface. Its duct (Wharton's) is 2 inches long and opens at the summit of a papilla by the side of the frenum linguae. The blood supply is received from branches of the facial and lingual arteries. Nerves reach it from the submaxillary ganglion of the sympathetic and the mylohyoid branch of the inferior dental.

Sublingual Gland—This is the smallest, weighing about 2 drams. It is placed under the mucous membrane at the floor of the mouth and is almond shaped. Its ducts (ducts of Rivinus, 18 to 20 in number) open separately on the floor of the mouth, generally one or two being joined and called Bartholin's ducts, which in turn join Wharton's duct. The blood supply is from the sublingual and submental arteries. The gustatory nerve from the posterior division of the inferior maxillary, supplies the gland.

The structure of these glands is that of the compound racemose type joined by dense areolar tissue, ducts and vessels. The secretion is alkaline, watery and contains ptyalin, which acts on the starch in food changing it to dextrose or grape-sugar.

Pathology—Not much is known of the pathology of mumps. The salivary glands are swollen. Of the entire series, one gland was removed on mistaken diagnosis. It showed a normal gland structure. Suppuration occurred in one case. It is questionable whether there was real gland suppuration here, or cellulitis of the tissues of the neck, with necrosis. Cervical and inguinal adenitis are not infrequent. The thyroid¹ gland may become enlarged during the disease. There were six cases. None of the other features of goiter appear, however. Neurotic manifestations suggest intracranial glandular involvement. In one case, in a woman, an axillary gland was swollen, producing breast pain. The pancreas is involved in some mysterious way. It may be the seat of edema or the glands at the hilus of the liver may enlarge. Except by one or the other or both of these theoretical pos-

¹ Major Sailer thinks it likely that these may have been cases of thymus rather than thyroid involvement. They have, however, not been carefully studied, unfortunately.

head was drawn back and dulness when it was brought forward. The skin showed slight edema which Major Sailer attributed to cutting off the lymph supply by the inflamed thymus. Roentgenograms showed a shadow behind the upper part of the sternum, which Major Wheat interpreted as an enlarged thymus.

One case of frontal sinusitis has been recorded. It is difficult to associate this with mumps etiologically. The glands involved in our cases have been as shown in Table 1.

Pathologic conditions associated with mumps were as shown in Table 2.

TABLE 2—PATHOLOGIC CONDITIONS ASSOCIATED WITH MUMPS

Condition	At or Before Onset, Cases	Developed During Onset, Cases
Measles	12	2
"Cold"	Very common	Very common
Bronchitis	13	14
Pterygium	1	0
Influenza	2	1
Laryngitis	6	0
Pneumonia	5	4
Bronchopneumonia	1	1
Tonsillitis	2	0
Malaria	1	0
Syphilis	1	0
Complications of mumps	To be mentioned separately	

Incubation Period—This was definite in only two cases. Nurse M. was put on duty in a mumps ward January 10 and developed mumps January 24. Miss H. developed mumps February 26, having left her last case February 3. These are periods of two and three and one half weeks, respectively. Osler says that the period is from two to three weeks. In our experience, this has been generally undeterminable.

ETIOLOGY

1 *The Virus*—Thus far the causative factor of mumps has not been definitely determined. Herb has implicated a diplococcus, which, when injected into Stenson's duct in monkeys, produces the disease. Attempts at isolation of an organism were initiated at Major Sailer's suggestion. These attempts have failed. Smears from the region of the orifice of the duct in the cheek revealed a spirillum, smaller and more slender than the *treponema pallidum*, in a few cases.

sibilities, it is difficult to explain the jaundice, abdominal pain and vomiting of pancreatitis. Orchitis is frequent. The testicles are swollen, both or one, and tender. They may each reach the size of a man's fist. The scrotum is always red and tense. Epididymitis often precedes the orchitis. A kidney bean shaped and sized swelling in the epididymis occurs sometimes before the testicle swells. Major Sailer emphasizes the fact that the epididymitis of mumps is not characterized by the exquisite tenderness which obtains in gonorrheal infection and that the testicle is very tender. Prostatitis is not common, but occurs and may be responsible for retention of urine.

TABLE 1—SHOWING THE GLANDS INVOLVED

Glands Involved	Cases
Both parotids alone	2,747
Parotid, right	554
Parotid, left	627
Both submaxillaries alone	16
Right submaxillary alone	7
Left submaxillary alone	11
Both parotids and both submaxillaries	128
Both parotids and right submaxillary	38
Both parotids and left submaxillary	30
Both parotids and both sublingual	9
Both parotids and right sublingual	1
Both parotids and left sublingual	1
Both parotids, both submaxillaries and both sublinguals	10
Both parotids, both submaxillaries and left sublingual	1
Both parotids, left submaxillary and left sublingual	1
Left parotid, left submaxillary and left sublingual	1
Left parotid, both maxillaries and both sublingual	1
Right parotid, left submaxillary and left sublingual	1
Both sublinguals alone	1
Left sublingual alone	1
Left sublingual and left maxillary	1
Right sublingual and right submaxillary	1
Right parotid and left submaxillary	11
Right parotid and both submaxillaries	2
Right parotid and right submaxillary	24
Left parotid and right submaxillary	10
Left parotid and left submaxillary	26
Summary	
a Parotid glands involved in one way or another	4,243
b Submaxillary glands involved in one way or another	440
c Sublingual glands involved in one way or another	20

Finally there are a few cases in which mumps expresses itself by a general swelling of the neck and chest like Hodgkin's disease, a doughy gelatinous mass. Cases of this sort have been noted by Lieutenant Hathcock and Lieutenant Groover. There is no tenderness. The tissues are soft and elastic and are easily agitated. Major Sailer has called attention to a case of possible thymus enlargement. There was some swelling presternally and also in the tissues of the neck. There was alteration in the percussion note over the manubrium on change of position of the head, tympany being present when the

head was drawn back and dulness when it was brought forward The skin showed slight edema which Major Sailer attributed to cutting off the lymph supply by the inflamed thymus Roentgenograms showed a shadow behind the upper part of the sternum, which Major Wheat interpreted as an enlarged thymus

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This was not constant, and it was concluded that the organism was the ordinary *Spinochaeta dentium*. Wight's tubes were next introduced into the orifice and smears made of the clear fluid which exuded, with negative results. At Major Sailer's suggestion, the parotid gland was aspirated with an ordinary hypodermic syringe, under aseptic conditions, one half inch below the ear. The few droplets of clear salivary secretion obtained in this way were planted on the following mediums: broth, plain agar, blood agar, human serum agar, Loeffler's medium, centrifugalized milk with a layer of cream on top, and agar covered with sterile liquid petrolatum—the last two being partially anaerobic. The results in all cases were negative, except on one occasion in which a pellicle was produced in ordinary bouillon, which showed very small cocci in flat masses. This was not reproducible, and it was concluded that the pellicle was the ordinary one which at times occurs in broth without inoculation. Smears from aspirated contents of the glands were negative. Major Sailer was very desirous of inoculating the testes of animals with the secretion, but, unfortunately, none were to be obtained. Major Thayer, on a visit to Camp Wheeler, suggested the use of salivary mediums for culture. This too, unfortunately, was not tried, due to press of work in the laboratory. It is an excellent idea and should be exploited. Noguchi's symbiotic tissue medium was not used because it could not be obtained. At my request a few tubes of 2 per cent glucose agar and human serum were sent down by Dr Libman from New York. Two thirds of the agar were mixed with one third serum (after melting the agar) and the tubes inoculated with the secretion aspirated from the parotid gland, and also with the blood of a patient who had developed orchitis. The tubes were rendered anaerobic by the addition of a layer of plain agar, on cooling of the mass. These ingredients were used by Dr Plotz in isolating the organism in his typhus work. Four days after inoculation no results had appeared.² It is to be concluded therefore that the virus does not grow on ordinary mediums. Inoculations intraperitoneally into mice and guinea-pigs by Lieutenant Lewis of the aspirated contents of the parotid were negative. Thanks are due and gladly given to Captain Wilson and Lieutenant Ross for their kindness and assistance in the laboratory.

2 *Contact*—There must necessarily be some influence exerted on the development of mumps by contact, otherwise the epidemic would not occur, and yet of the physicians, nurses and corps men, only

2 On the sixth day a lenticular colony, grayish yellow in color, about the size of a millet seed appeared in the middle of the medium. There were fine ciliary radiations from it. Smears showed diplococci which will be described subsequently.

twenty-nine all told took the disease—persons who had been in intimate contact with it. Five were nurses, five physicians, and nineteen corps men, of whom four were not Base Hospital men, but belonged to ambulance companies

3 *Age*—The age incidence was from 16 to 25 years

4 *Sex*—Only five cases were in women (Eighty nurses in hospital were the only material)

5 *Service*—The length of service in 95 per cent of the cases was two months

6 *Habitat*—The fact that most of the men lived on farms nearly all their lives may have had some bearing on the epidemic. They had not been accustomed, like their urban cousins, to epidemics of any sort, and therefore, from lack of immunity, geographically furnished good soil for the virus

8 *Previous Condition*—A factor of some importance was the previous condition of the men. They had been below par physically

7 *Season*—The winter months, October to March, were included

9 *Immunity*—One attack does not confer immunity. Forty-seven patients gave a previous history of mumps, in the majority of which cases the gland on the side opposite to that of the present attack had been involved, but three patients had the same gland involved twice. One patient had mumps three times. The intervals varied from two weeks to fourteen years. Lieutenant Hathcock doubts these histories and claims that one attack protects. One hundred and forty-four cases, or 33 per cent, had more glands develop during course than were involved at onset. The majority were right and left parotids, respectively. The intervals varied from one to seventeen days, the average was nine days, most frequently only twenty-four hours. Relapses occurred in six cases. The interval was from two to three weeks

SYMPTOMS

The symptoms of mumps show many varied but also some constant features

1 *Prodromal*—Often a diagnosis of mumps may be reached before there is any swelling from the following symptoms

a A feeling of stiffness in the jaws

b Difficulty in opening mouth

c Condiments, especially sour ones, cause a "drawing" sensation in the jaws

d Dry mouth may occur at first. No sense of taste and no secretions. There may be salivation. Thirst is at times unquenchable

e The orifices of Stenson's duct pout and a pinkish area appears around them. They may gape wide open. This is especially noticeable in unilateral cases. A Wright's tube is introduced with ease, whereupon a clear fluid fills it.

f The most diagnostic prodromal sign, pathognomonic, in fact, was first noted by Lieutenant Hathcock, who has personally observed and treated over 2,000 cases, and who is, from the standpoint of knowledge gained by close clinical observation of the disease, probably the best authority on mumps in the United States. The sign is tenderness just beyond the angle of the jaw on running the finger toward the angle, under the mandible. If the parotid gland is at all involved, the patient winces with pain. This occurs before any swelling can be made out. It is proper and fitting—much as eponyms are held by some to be improper—that this sign go down in the literature as Hathcock's sign. It is almost constant, it is early, it is definite and it is exclusive, therefore it is diagnostic, like Koplik's spots in measles.

2 *The Onset*—The symptoms of onset of mumps have been many and varied.

a Onset with no symptoms

b Onset with gastric disturbances and features suggesting pancreatitis

c Onset with pancreatitis, orchitis and urethral discharge. This occurred in two cases before the glands swelled. Lieutenant Byrne has seen one of them.

d Onset with features of acute laryngitis and bronchitis. This was rather common in Lieutenant Hislop's series. It was especially marked during the time when measles and mumps coexisted. Cough was a marked feature. Also pain in the sternal region.

e Grippy onset, with fever, headache, malaise, bone pains and aches, and sore throat was very common.

f Onset with inguinal and testicular pain and backache—although orchitis did not develop—was not infrequent.

g The ordinary onset is with pain and swelling in the jaws, stiffness, difficulty in opening the mouth, slight malaise and mild fever. According to Lieutenant Hathcock, the pain in parotid cases is greater than in submaxillary cases, because of the proximity of the tissues to the bone in the former and to the soft elastic tissues of the neck in the latter case.

3 *The Course*—This is variable. Special symptoms of all sorts arise. Elevation of temperature is not constant, fever occurred in over 80 per cent of the cases, however (Figs 1 and 2).

The temperature in all cases showed a rise and fall in severity, corresponding to the epidemic proper. The range of fever is from 99 to 106 F, most commonly 99 to 101. The duration of the fever is from one to twenty-four days, the average is four days. About twenty-four hours before onset of a complication the temperature rises from one to three degrees and lasts about five days. Subnormal

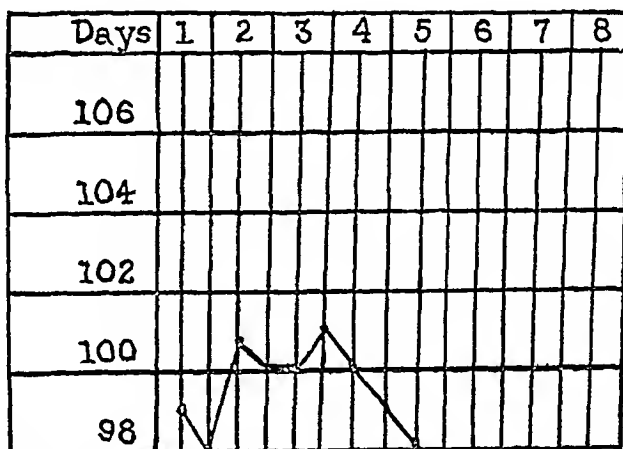


Fig 1—Temperature curve in an ordinary case

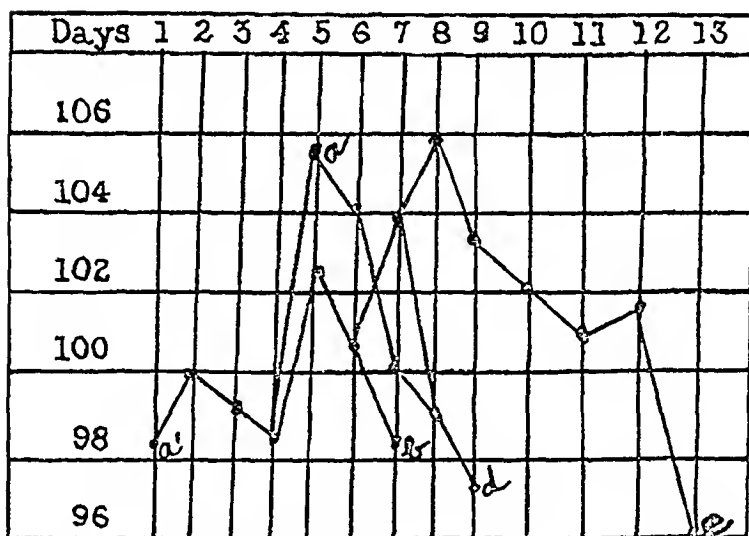


Fig 2—Temperature curve in orchitis accompanying mumps a'-b, most common, a-e, all occur

temperature may occur with cessation of the complication. The temperature may be 106 F without obvious cause.

Vomiting, nausea, and pain and tenderness in the testicles may occur without apparent cause.

Tenderness in the epigastrium, jaundice and vomiting suggest pancreatitis.

Urinary retention may develop. Lieutenant Urey removed 32

ounces by catheter in one case. Sometimes prostatitis is associated with retention. Lieutenant Hislop is of the opinion that retention is reflex from the pain in the testicles and lumbar regions. Polyuria is not common.

Tender breasts occurred in one man and in one woman.

The patient may be doing well, apparently, and without cause develop the most marked nervous disturbances. Fainting, cold sweats, sense of collapse, diarrhea and excessive irritability may occur. Convulsions are rare, only one patient presenting a few jerky movements.

TABLE 3—PERCENTAGES

Cases	Poly morpho nuclears	Lymphocytes		Endothelials		Eosino phils	Baso phils	Total Count
		Small	Large	Trans	Others			
Normal (Stitt)	67.5	25.0	4.0	3.0	1.5	1.5	0.4	7,125
Orethritis	60.2	30.2	4.3	1.7	1.8	1.8		10,730
Uncomplicated	51.9	36.4	2.0	3.1	3.0	3.6		7,000
Average (all cases)	54.2	34.7	2.6	2.7	2.7	3.1		8,000

TABLE 4—TOTAL CELLS PER CUBIC MILLIMETER

	Orethritis	Uncomplicated	Total
Number of cases	3	8	11
Total leukocytes	10,730	7,000	8,000
Polymorphonuclears	6,470	3,600	4,300
Lymphocytes			
Small	3,240	2,570	2,800
Large	460	140	210
Total	3,700	2,710	3,010
Endothelial			
Transitional	180	220	210
Others	190	210	200
Total	370	430	410
Eosinophils	100	260	240

All grades of deafness have been present. One patient described his ears as "wooden." Rarer symptoms, but occurring in a sufficient number of cases to warrant their notice, were epistaxis, herpes and dysphonia. A husky or small voice was most frequent.

4 *Laboratory Findings*—The blood was examined in about 200 cases. Of 105 white counts made by Lieutenant Lewis, the average figure was 8,800, the extremes being 6,000 and 13,000. The accompanying tables and curves show the results obtained by Lieutenant Belding's blood counts in mumps (Tables 3, 4 and 5).

Lieutenant Belding concludes

1 *Total Count*—The uncomplicated cases showed approximately a normal total leukocyte count (7,060). In orchitis, there is a definite leukocytosis (10,730), which is largely polymorphonuclear in character, that is, 6,470 polymorphonuclear cells per cubic millimeter, nearly double the number (3,660) in the uncomplicated cases, whereas the lymphocytes show a smaller increase, that is, 3,240 vs 2,570, or a corresponding gain of one quarter.

TABLE 5—NUMBER AND PERCENTAGE OF CELLS

	Orchitis	Uncomplicated	Total
Number of cases	8	8	11
Total average count	10,730	7,060	8,060
Highest	14,000	12,700	14,000
Lowest	7,400	4,030	4,030
Polymorphonuclears, per cent	60.2	51.9	54.2
Highest	82.0	61.5	82.0
Lowest	46.4	41.0	40.4
Lymphocytes			
Small	30.2	36.4	34.7
Highest	40.6	50.0	50.0
Lowest	11.0	27.0	11.0
Large	4.3	2.0	2.6
Highest	8.0	4.0	8.0
Lowest	2.0		
Total	34.5	38.4	37.3
Highest	43.6	51.0	51.0
Lowest	13.0	27.7	13.0
Endothelials, per cent			
Transitionals	1.7	3.1	2.7
Highest	3.0	4.0	4.0
Lowest	1.0	2.0	1.0
Others	1.8	3.0	2.7
Highest	4.0	7.0	7.0
Lowest		1.0	
Total	2.5	6.0	5.4
Eosinophils, per cent			
Highest	1.8	3.6	3.1
Lowest	5.5	6.0	6.0
Lowest		1.0	

2 *Polymorphonuclear Neutrophils*—The polymorphonuclear leukocytes show a relatively higher percentage in the orchitic than in the uncomplicated cases. In the latter, the average (51.9 per cent) is somewhat less than the normal (67.5 per cent) as given by Stitt. In the orchitic cases, the percentage of polymorphonuclears is 60.2, which is less than is ordinarily found with leukocytosis of pyogenic infections.

3 *Lymphocytes*—Conversely, the relative percentage of lymphocytes, 38.4 per cent in uncomplicated and 34.5 per cent in orchitic cases, is above the normal, which varies from 22 to 36 per cent. The highest orchitis case gave 43.6 per cent, the lowest 13 per cent, while

in the simple cases the highest was 51 per cent and the lowest 27.7 per cent. Therefore, it may be concluded that there is a slight tendency toward lymphocytosis in mumps, but in view of the small number of cases here considered (11) a definite statement cannot safely be made when the margin of increase is so small.

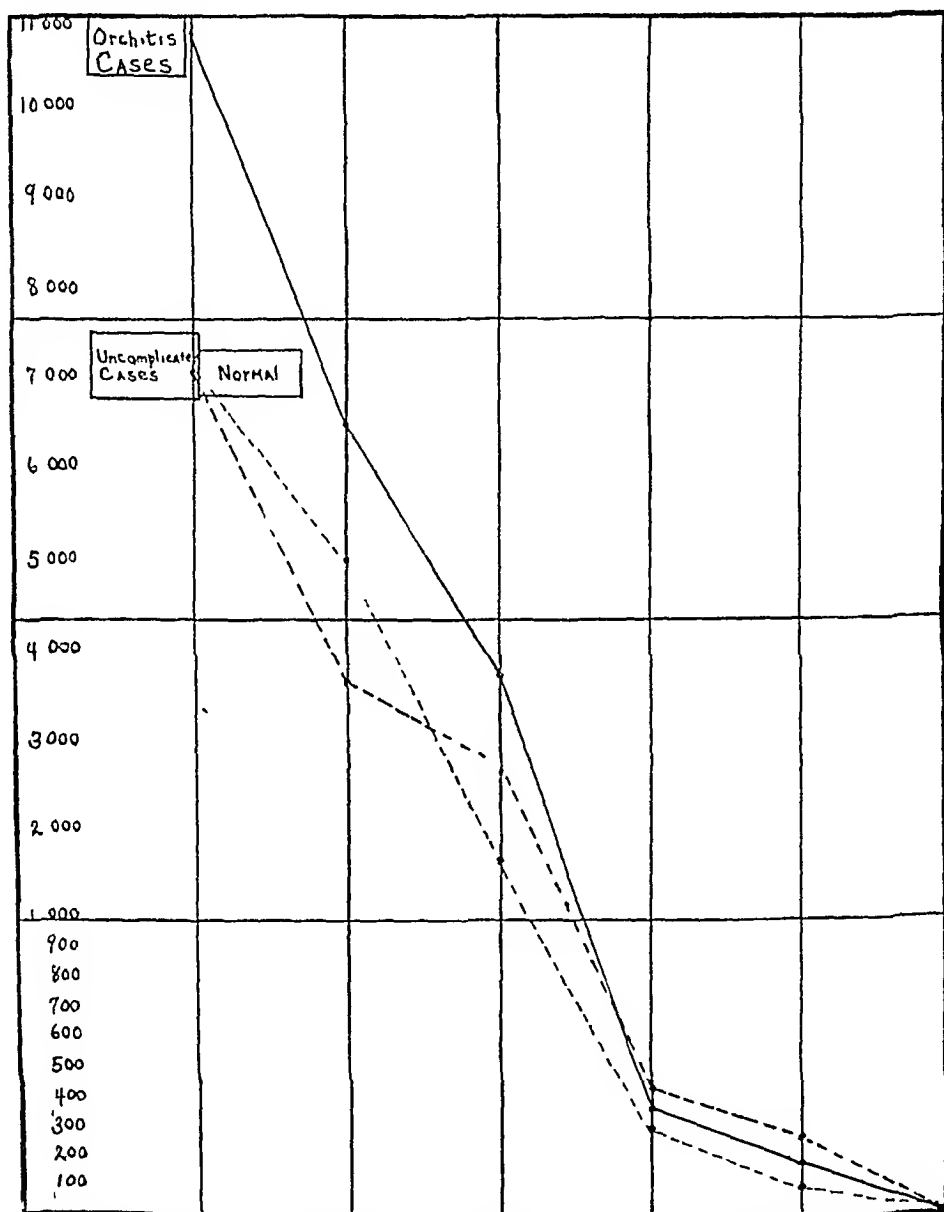


Fig 3—Curves showing leukocyte and differential count in mumps uncomplicated (eight cases), and in cases complicated by orchitis (three cases), from Feb 7, 1918, to Feb 18, 1918

4 *Endothelials*—This class gives a slight increase above the average, but falls within normal limits

5 *Eosinophils*—The increase in eosinophils is probably due to intestinal parasites (hookworm) and has nothing to do with mumps

Red blood cells averaged 4,800,000, average hemoglobin 75 per cent. The urine in thirty cases — all kinds — was normal. Bile was present in one case of pancreatitis with jaundice, which cleared up on disappearance of the icterus (Lieutenant Lewis.)

5 *The Physical Signs of Mumps*

- 1 Hathcock's sign
- 2 Pouting and pinkness of the orifices of Stenson's ducts
- 3 Swelling of the face in the parotid region
- 4 Doughy elasticity of the swelling
- 5 Exudation of secretion from Stenson's duct on pressure of the gland externally. This was noted by Lieutenant Hathcock and others. The physical examination of the rest of the body is usually negative except in complicated cases.

COMPLICATIONS

1 *Orchitis and Epididymitis* — Of 4,397 cases carefully considered, 611 had testicular involvement of various kinds, or 13.91 per cent.

TABLE 6 — COMPLICATIONS

Complications	Number of Cases
Orchitis, bilateral	102
Orchitis, right	231
Orchitis, left	221
Orchitis, side not mentioned	40
Epididymitis, right	4
Epididymitis, left	1
Epididymo orchitis, right	9
Epididymo orchitis, left	3
Total	611

Perhaps epididymitis was more common than this table indicates, because of the fact that the ward surgeons did not pay special attention to the orchitis cases beyond noting that the testicles were involved.

Thirty-seven cases developed orchitis on the side opposite to the glandular involvement of the face. Close questioning in many similar cases revealed a former infection on the other side of the face also. It is the general impression held by the ward surgeons that these thirty-seven cases may fall in this category. At any rate, the vast majority had the testicles involved on the same side as the facial swelling in unilateral cases.

Orchitis is the most frequent and most severe complication of mumps. It may occur in any period of the disease, even before the

parotid swelling, and be accompanied by urethral discharge. Orchitis begins from the third to the sixth day and lasts a variable period — from five to ten days. In not a few cases the epididymis is swollen before the testicles. Single glandular involvements were complicated by bilateral orchitis and vice versa. Orchitis makes the patients sick. There is a rise in temperature sometimes to 106 F, usually to 102. Vomiting and nausea are frequent. The patient may be covered with profuse warm perspiration. The face is anxious. Sharp shooting pains in the testicles and inguinal regions occur. There may be severe backache. With the rise in temperature, a leukocytosis is usually present from 11,000 to 14,000, as shown by Lieutenant Belding and Lieutenant Lewis. Polyuria may be present. Lieutenant Dalton has obtained histories of nocturnal pollutions in these cases which he believes are due to reflex irritations. Lieutenant Hathcock, on the other hand, thinks that continence is responsible for the condition. At any rate, close observation of this symptom has not shown it to be a constant feature. After a miserable period of from twenty-four to forty-eight hours, the testicles enlarge and are exquisitely tender. The course of orchitis is variable. After three to ten days, the testicles involute, the fever subsides, the pain and malaise depart, urination is free, the appetite returns and the patient is to be found more frequently at the canteen than in the ward.

2 *Otitis Media* —Suppurative otitis media occurred in 20 cases of 4 397, or 0.45 per cent.

TABLE 6—EAR INVOLVEMENT

Ear Involved	Number
Otitis, bilateral	4
Otitis, right	11
Otitis, left	5

Suppuration may be profuse or mild. Pain is of varying degree of intensity. There is a rise in temperature of several degrees and at times dysphonia — nasal voice occurs. Fainting and vertigo may come on. Mastoiditis occurred in three cases which were not recorded among the total number, and were operated on by Captain Swan.

3 *Pancreatitis* —Whether an entity or a syndrome, the symptom group is real. The patient becomes extremely ill. There is intense nausea and anorexia. Pain and tenderness in the epigastrium rapidly supervene. The temperature rises slightly. Diarrhea may occur or the patient may become jaundiced, four cases of this kind having been noted. The spleen was palpable in one case, but the patient gave a malarial history. The attack is like acute catarrhal jaundice, except

that it lasts only from three to five days. Pancreatitis occurs from the fifth to the eighth day, as a rule, but this varies. There were fourteen cases, or 0.31 per cent.

4 *Pneumonia*—Five cases of lobar and one case of bronchopneumonia occurred during mumps. Major Sailer feared an increased pneumonia admission rate as a result of mumps, just as happened after measles, but fortunately this did not occur. Mumps has apparently little effect on the respiratory system from the standpoint of lowering the resistance to pneumonia.

5 *Bronchitis*—There were nine cases of the ordinary type and course.

SEQUELAE

It is premature to note any sequelae in our epidemic. Sexual vigor is retained according to Osler, even with both testicles atrophied. It is not definite whether permanent deafness results from the otitis media.

DIAGNOSIS

The diagnosis of mumps is the simplest to make, and in mild cases very easy to overlook. The following are diagnostic:

1. Hathcock's sign
2. Pink and pouting orifices of Stenson's ducts
3. Swelling and tenderness of the salivary glands
4. Exudation of secretion from duct on pressure of gland
5. Pain or peculiar "drawing" sensation on eating sour food

Differential Diagnosis

<i>Mumps</i>	<i>Ordinary Toothache with Edema</i>
1. Parotids enlarged	1. Parotid not enlarged
2. Hathcock's sign positive	2. Negative
3. May be dry mouth	3. May be salivation
4. Gums not swollen	4. Gums swollen
5. Perverted taste and pain if sour food is eaten	5. Neither
<i>Mumps</i>	<i>Epuhs</i>
1. Fever	1. None
2. Gums O. K.	2. Tumor
3. Parotids swollen	3. Not swollen
4. Epidemic	4. Not epidemic
<i>Submaxillary Mumps</i>	<i>Tonsillitis with Cervical Glands</i>
1. Epidemic	1. Not epidemic
2. Tonsils normal	2. Inflamed
3. Swelling is under center of mandible	3. Further back

Course of Disease—In uncomplicated cases, in a week the infection has subsided. The average duration—all cases—has been fourteen days, limits, two to thirty-one days. A complication prolongs the course about a week. A normal patient may suddenly develop orchitis or otitis. If pancreatitis occurs, the course is prolonged about four days. Pneumonia and bronchitis lengthen the disease by their own course.

PROGNOSIS

Of the entire epidemic, the only death was due to pneumonia. Complications are temporary. A patient without facial swelling who presents Hathcock's sign and pouting orifices of Stenson's duct will develop mumps. If, on the third day, the patient has a rise in temperature, pain in testicles, abdomen and back, with vomiting and perspiration, he may develop orchitis or pancreatitis or both. Deafness does not mean otitis. Mastoiditis has the same prognosis as in any other condition.

TREATMENT

A Prophylaxis—1 Careful isolation of cases for a period covering their infectivity—three weeks.

2 Of orchitis. Orchitis occurred no more frequently in the series studies by Lieutenant Byrne and Lieutenant Sherrill, whose patients got up for meals and walked about generally, than it did in Lieutenant Groover's series, whose patients stayed in bed throughout the course. Lieutenant Lewis has found that careful sterilization of the hands and protection of the glans penis did not reduce the incidence of the complication. At Major Sailer's suggestion, alternate patients were put on hexamethylenamin as admitted, 5 grains four times daily. Lieutenant Hathcock's figures show no improvement after the drug, and he concludes that "hexamethylenamin produces no perceptible results as to prevention of orchitis." Considering all figures, however, there is some benefit. Before the exhibition of hexamethylenamin, 304 cases occurred and 307 afterward, but there were only 52 cases of orchitis in which the hexamethylenamin was given before the patient had orchitis—a reduction in number by 33 per cent.

3 Of otitis. Of all measures, 2 per cent phenolized glycerin instituted routinely—drops 2 being dropped into each nostril twice daily—at Major Sailer's suggestion, has proved the most beneficial. Before phenol in glycerin treatment began, there were seventeen cases, afterwards but three.

B Treatment Proper—The treatment proper of mumps is palliative, symptomatic and expectant. Our treatment has been

1 Two compound cathartic pills on night of admission and saline in morning to insure free catharsis.

- 2 Dobell's gargle for mouth
- 3 Hot application and camphorated oil to swelling
- 4 For the pain and nervousness, acetyl salicylic acid and bromids
- 5 For fever, acetyl salicylic acid and acetanilid
- 6 Phenol, 2 per cent in glycerin, 2 drops in each nostril, should be administered twice daily
- 7 Hexamethylenamin has some value in reducing the incidence of orchitis, 5 grains four times daily
- 8 For orchitis, support and counterirritation, any mild counter-irritant will do *a* ice bag, *b* 10 per cent ichthyol ointment, *c* guaiacol carbonate was used in a few cases with fair results, and finally,
- 9 Rest in bed, which is the best treatment

A STUDY OF EIGHT CASES OF ACUTE NEPHRITIS*

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INTRODUCTION

A strictly pathologic interpretation of the term acute nephritis must mean acute inflammation of the kidneys, an inflammation primary or superimposed on a chronic process. There are, however, certain acute clinical pictures in which edema, albuminuria and other so-called renal findings may occur independent of real inflammatory disease. Hence a more consistent name for this group would be acute renal syndrome, and the cases presented here are so considered, although in certain of them actual inflammation was probably present. Moreover, in some of the cases one feels that possibly the renal manifestations are entirely secondary to a systemic disease, as is the chlorid retention of pneumonia. Two cases (7 and 8) are definitely chronic (from their histories), but they differ so strikingly from each other and are so similar in many ways to the truly acute cases that they are included for purposes of comparison. The "acuteness" of the other cases (1 to 6) is based on the absence of previous renal symptoms, for five of the six were intelligent people whose histories were quite reliable, and the sixth was partially confirmed by a daughter who is a trained nurse. That these are cases of renal edema, the absence of other causes for edema makes clear.

METHODS

The urinary chlorids were estimated by the Volhard method, plasma chlorids by the McLean and Van Slyke¹ method, blood urea and urine urea by Van Slyke and Cullen's² modification of Marshall's method. Practically all determinations were made in duplicate. The renal test day consisted in confining the fluids to the meals and collecting the urine in the periods described by Mosenthal.³ The metabolism department of the Presbyterian Hospital weighed the patients and was in charge of the urine collection. All foods were weighed and fluids measured. The phenolsulphonephthalein was allowed five minutes for appearance time and the two-hour excretion determined.

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* From the Medical Clinic, Presbyterian Hospital, and the Coolidge Fellowship in Medicine, Columbia University.

1 McLean and Van Slyke *Jour Biol Chem*, 1915, **21**, 361.

2 Van Slyke and Cullen *Jour Biol Chem*, 1914, **19**, 211.

3 Mosenthal *THE ARCHIVES INT MED*, 1916, **16**, 733.

The urea and chlorid indexes were determined over two-hour periods and calculated according to McLean's⁴ formulae, with this exception, a constant weight was used for the entire period of observation, a weight as near the patient's normal as could be estimated. It seems obvious that a change in the index due to the loss of 40 pounds of edema would not express a true change in renal function.

REPORT OF CASES

CASE 1—No 342213 Woman, aged 27, admitted March 6, 1917. Complaint, headache for five days.

Family History—Mother died of tuberculosis.

Personal History—Malaria at 22 years, tonsillitis at 25 and 26 years, has a rash when she eats strawberries, dyspnea on exertion for four months, no nocturia or any renal symptoms.

Present Illness—Edema of ankles for two or three weeks, frontal headache twelve days before admission, returning again five days before admission and continuing up to admission, no other symptoms, no urinary abnormalities.

Physical Examination—Slight general edema, some pyorrhea, large red tonsils, heart moderately enlarged to the left, blood pressure, 188/150, suggestion of fluid at left base, right kidney palpable, sinuses negative, eyegrounds normal, Wassermann negative. Blood hemoglobin, 91 per cent, red blood corpuscles, 4,980,000, white blood corpuscles, 10,000. Urine specific gravity, 1.011, albumin, faint trace, hyaline and granular casts, no red blood corpuscles. Nephritic test day specimen, 1,455 cc, specific gravity, 1.008-1.010, night specimen, 765 cc, specific gravity, 1.013.

Course—Under treatment the edema disappeared in two weeks and in three weeks the blood pressure was 130/90, during her five weeks in the hospital the specific gravity of the urine varied from 1.008 to 1.020 and at no time were there red blood corpuscles in it.

Readmitted June 20, 1917, for functional study. Aside from tiring very easily, the patient feels quite well, no edema, blood pressure, 122/70. Blood red blood corpuscles, 5,500,000, hemoglobin, 112 per cent, white blood corpuscles, 9,400. Urine specific gravity, 1.012-1.015, albumin, trace, 1 hyaline cast. Renal function entirely normal throughout.

Phenolsulphonaphthalein, 60 per cent, Ambard, 111, blood urea, 0.20 gm per liter, actual plasma chlorid, 6.03 gm per liter, calculated plasma chlorid, 5.97 gm per liter, threshold, 5.67 gm per liter.

O. P. D., July 29, 1917. Blood pressure, 130/80, no edema.

Feb 24, 1918, patient reported to be sick in bed out of town, nature of illness unknown.

CASE 2—No 34165 Man, aged 27 years, admitted Feb 27, 1917. Complaint, swelling of legs and ankles for two days.

Family History—Father had rheumatism, mother died at 52 years of kidney trouble.

Personal History—Rheumatic fever when a child, hives at 15 years, no renal or cardiac symptoms before present illness.

Present Illness—Nocturia for two or three weeks, slight cough for one week, three days prior to admission, frontal headache lasting one day, next day, while bathing, noticed that his feet were swollen, no nausea, urinary changes or dyspnea, some palpitation.

Physical Examination—Marked general edema, severe pyorrhea, heart slightly enlarged to the left, blood pressure, 154/90, ophthalmoscopic examina-

⁴ McLean Jour Exper Med, 1915, 22, 212

tion negative except for slightly hazy disks, blood culture and Wassermann, negative Blood hemoglobin, 70 per cent, red blood corpuscles, 3,570,000, white blood corpuscles, 7,600 Urine specific gravity, 1 033, albumin, very faint trace, few red blood corpuscles, occasional hyaline and granular cast Nephritic test day specimen, 598 c c, specific gravity, 1 011-1 028, night specimen, 1,315 c c, specific gravity, 1 015

Course—After nine days with restriction of salt, water and nitrogen the edema disappeared, the blood pressure dropped to 118/80 and the urine became perfectly normal except for an occasional hyaline cast

March 20—Hemoglobin, 70 per cent, red blood corpuscles, 4,020,000

May 31, 1917—Urine albumin, negative, microscopic examination, negative, Ambard, 470, blood urea, 0 15 gm per liter Actual plasma NaCl, 6 25 gm per liter, calculated plasma NaCl, 6 09 gm per liter, threshold, 5 78 gm per liter

Feb 4, 1918—Patient in France with the American Expeditionary Forces, said to be in good health

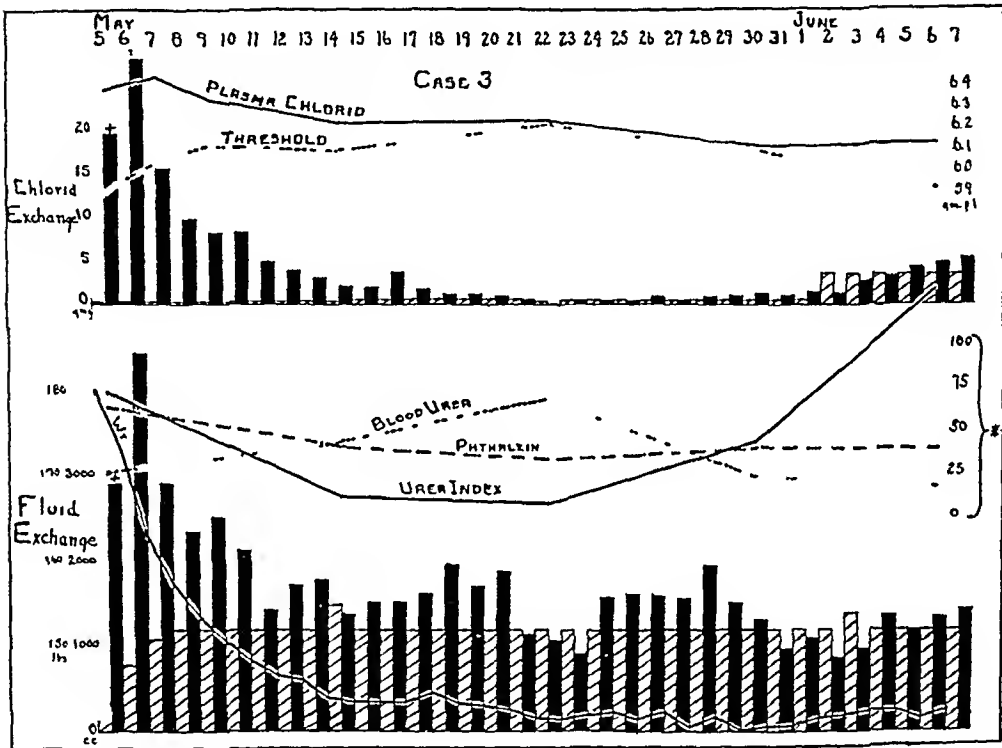


Chart representing chlorid and fluid exchange in Case 3 * = mg per 100 cc for blood urea, per cent for phenolsulphonophthalein, indirect for urea index (McLean)

CASE 3—No 34795 Man, aged 35, admitted May 4, 1917 Complaint, headache and swelling of body for two weeks Family history negative

Personal History—Works as a brakeman and is subjected to considerable exposure, has "grippe" every winter, has had frequent frontal morning headaches since childhood, tonsillitis and quinsy six years prior to admission and tonsillitis again four years prior to admission, tonsillectomy one year prior to admission, no sore throat since, nocturia for four months, no dyspnea or edema

Present Illness—Onset three weeks prior to admission with coryza, severe headache, pains in chest—"grippe," he worked on for a week and then went to bed for three days, on returning to work his body began to swell, he became

dyspneic and his urine became scanty and "dark brown" in color, for the previous ten days he had been on a diet of milk, cereals and broth and for the previous five days his urine had been clearer and of larger quantity, no nausea or vomiting, edema had been decreasing in the previous four days

Physical Examination—Diffuse edema, mainly below fourth rib, slight signs of fluid at both bases, mild coryza, heart, lungs and abdomen normal, blood pressure, 145/95, Wassermann, negative Blood hemoglobin, 70 per cent, red blood corpuscles, 4,240,000, white blood corpuscles, 11,300 Urine specific gravity, 1.017, albumin, faint trace, occasional hyaline casts, no red blood corpuscles Nephritic test day specimen, 852 c c, specific gravity, 1.010-30, night specimen, 505 c c, specific gravity, 1.019

Course—Under treatment the edema disappeared and the blood pressure reached normal (122/80) in six days, July 3 the blood was, red blood corpuscles, 5,400,000, hemoglobin, 75 per cent

Oct 31, 1917—The patient feels perfectly well and is at work, no dyspnea, edema or nocturia, blood pressure, 120/60

January, 1918—Feeling fine, working as a brakeman again, blood pressure, 108/60, no symptoms at all Red blood corpuscles, 4,576,000, white blood corpuscles, 11,800, hemoglobin, 97 per cent Urine albumin, very faint trace, microscopic examination, negative Ambard, 65, blood urea, 0.2 gm per liter, actual plasma NaCl, 6.6 gm per liter, calculated plasma NaCl, 5.89 gm per liter, threshold, 6.33 gm per liter

CASE 4—No 34213 Woman, aged 26, married, admitted Feb 20, 1917 Complaint, swelling of face and feet, blood in urine for two weeks Family history negative

Past History—Frequent attacks of "grippe" the last five weeks prior to admission, four or five months prior to admission, fleeting attacks of dizziness, four months prior to admission, at night had an epileptic attack in which she bit her tongue and was unconscious for ten minutes A similar attack occurred five weeks and again six weeks later, no urinary or cardiac symptoms before present illness

Present Illness—Five weeks prior to admission the patient had an attack of "grippe" with sore throat, malaise, general pains, chills and fever, headache and sweats, was in bed five days, after being up about two days she noticed confluent red and blue streaks over her feet and legs to her knees and her feet were so sore that she could not walk, there was no scaling of the eruption, several days later she began to vomit everything, this lasted about two weeks but she did not go to bed, toward the end of this time she began to have swelling of the feet and face and dyspnea on exertion, and at about the same time she began to have blood in the urine These symptoms have continued to the present, occasional frontal headaches for the previous ten days, nocturia for the previous two or three weeks, her edema had begun to decrease a few days before admission

Physical Examination—Pale, slight edema of legs, fading purple spots on both legs and on outer side of left leg an area 6 cm in diameter indurated, inflamed and tender in center, bad teeth, large cryptic tonsils, heart slightly enlarged to left, with soft, blowing, systolic murmur at apex, blood pressure, 132/86, eyegrounds, normal, Wassermann, negative, roentgenogram of kidneys, negative, urine culture, negative Blood hemoglobin, 85 per cent, red blood corpuscles, 3,850,000, white blood corpuscles, 12,000 Urine grossly bloody, specific gravity, 1.016, albumin, trace, hyaline, granular and blood casts Nephritic test day specimen, 642 c c, specific gravity, 1.008-12, night specimen, 612 c c, specific gravity, 1.010

Course—The edema quickly disappeared but the hematuria persisted grossly for about three weeks and there was microscopic blood in the urine on discharge three months after admission, while in the hospital she had two typical epileptic seizures, blood pressure was between 105/76 and 130/78

Readmission, Nov 12, 1917 Feels fine and has gained greatly in strength, no edema, headaches or epileptic attacks, no urinary symptoms

Physical Examination—No edema, good color, heart unchanged, blood pressure, 105/75, red blood corpuscles, 4,700,000, hemoglobin, 85 per cent, white blood corpuscles, 11,400 Urine specific gravity, 1.028, albumin, very faint trace, no casts or red blood corpuscles, salt concentration, 0.76 per cent, phenolsulphonaphthalein, 67 per cent, Ambard, 72, blood urea, 0.26 gm per liter

CASE 5—No 34891 Man, aged 46, admitted May 14, 1917 Complaint, swelling of body for one week Family history negative

Personal History—The patient's low mentality and poor command of English made the history somewhat unsatisfactory, apparently quite healthy up to present illness, nocturia two or three times for all his life but no other symptom of renal disease, no scarlet fever, one brandy a day regularly

Present Illness—Onset one week before admission, with a severe headache that lasted for two days, on the third day he noticed the diffuse edema, on admission he complained of sore throat and slight cough of one day's duration, no history of dyspnea or urinary changes

Physical Examination—General edema and anasarca, very marked oral sepsis with gingivitis and ulceration, large heart with soft systolic blow at apex, blood pressure, 175/80, liver palpable, ophthalmoscopic, negative, Wassermann, negative Blood hemoglobin, 85 per cent, red blood corpuscles, 5,180,000, white blood corpuscles, 11,800 Urine specific gravity, 1.023, albumin, 1.5 per cent, many hyaline and granular casts, few red blood corpuscles

Course—On restriction of salt, nitrogen and water the edema disappeared, blood urea returned to normal from its high figure, 1.41 gm per liter, the blood pressure dropped to 130/66, and on discharge the urine showed no blood or casts During recovery red blood corpuscles went to 4,140,000 and hemoglobin to 65 per cent

June 22, 1917—Blood pressure, 160/90

Dec 29, 1917—Patient's family reports that he is perfectly well, he refuses to return for observation

CASE 6—No 34128 Man, aged 26, admitted Feb 24, 1917 Complaint, swelling of face for ten days Family history Mother died of tuberculosis

Personal History—Works as a compositor (eight years) but has always been very careful with the lead, Bell's palsy eight years prior to admission, with two exacerbations since, no sore throats, no cardiorenal symptoms before present illness

Present Illness—Onset ten days previous to admission, with swelling of face, two or three days previously he had a cough, for one day he had noticed swelling of the ankles, absolutely no other symptoms could be elicited

Physical Examination—General edema, residual right facial paralysis, carious teeth, large tonsils, few palpable glands in neck and axilla, heart enlarged to left, blood pressure, 178/112, ophthalmoscopic examination, negative, Wassermann, negative, roentgenogram of teeth and sinuses, negative, marked typus femininus, with soft skin, scanty body hair and transverse pubescence Blood hemoglobin, 79 per cent, red blood corpuscles, 4,350,000, white blood corpuscles, 7,600, no stippling Urine specific gravity, 1.017, albumin, heavy trace, hyaline and granular casts, few red blood corpuscles, lead negative

Course—Progressively downward, edema increased and hydrothorax and ascites developed, March 24, blood CO₂=24.8 mm Hg (acidosis was corrected easily with bicarbonate) April 11 his gums began to bleed and a week later he was twitching and irrational and diarrhea had set in, these symptoms continued until death April 21 the kidneys were decapsulated and the patient died twelve hours later Postmortem examination was not obtained

The blood pressure remained practically constant, the urinary picture did not change except that the specific gravity went as high as 1.022 at one time, the blood became anemic in type, red blood corpuscles, 3,300,000, hemoglobin, 65 per cent, the blood urea increased steadily. About one week before death a number of small ulcers about two to three mm in diameter appeared on both legs and thighs, they resembled small vesicles or pustules with the top scraped off.

The kidney at operation was about normal in size, with a smooth surface and an easily stripping capsule. The kidney tissue did not bulge when the capsule was cut. A small piece of kidney tissue was removed for microscopic examination. "The tissue was not very well fixed, but the lesion was very definite and striking. Every glomerulus was affected. Each showed more or less proliferation of the capsular epithelium. In some there was the characteristic crescent formation. Adhesions between the glomerulus and the capsule were common, and some of the glomeruli were partially organized. There was, in places, a considerable increase in connective tissue, especially in the neighborhood of the glomeruli. There was very little in the way of a cellular reaction and the few scattered cells seen in the interstitial tissue were chiefly of the mononuclear variety. A few polynuclears were noticed in some of the tubules. Tubular changes were not very marked, a good many were filled with a cellular debris with, in places, a little mixture of blood, and some were dilated. The vessels were practically unaffected.

"The lesion was essentially a glomerulonephritis. I should say that the process had been going on for some time, but in the absence of marked scarring, I should designate the lesions a subacute glomerulonephritis." This description of the section was kindly made by Dr. R. A. Lambert.

CASE 7—No. 33341—Woman, aged 25, single, admitted Dec. 31, 1916. Complaint, kidney trouble for four weeks. Family history negative.

Past History—Diphtheria at 19, with antitoxin, no reaction, frequent colds and sore throats, no edema or nocturia. Previous admission to this hospital April 25, 1914 (No. 13347), with the diagnosis "gastric ulcer and hematemesis", she improved on a Lenhartz diet and was discharged May 18, 1914, at this time she showed no edema, blood pressure, 100/78, heart 11.5 cm. to the left in fifth interspace, urine specific gravity, 1.016-37, albumin, faint trace, occasional hyaline cast. Patient still complained of some pain immediately after eating.

Present Illness—Edema of ankles for about four weeks, puffiness of face and swelling of abdomen for two weeks, weakness and mild morning headaches for about the same length of time, dull aching pain in lumbar region worse on right and on lying down, for about two weeks, no nausea, nocturia, dyspnea or eye symptoms, no definite history of hematuria, chill and fever the day before admission.

Physical Examination—Pale, slight edema of face, marked edema of legs, bad pyorrhea, tonsils deep and cryptic, heart 5 cm. to right in fourth interspace, 14 cm. to left in fifth, blood pressure, 154/102, few fine râles at both bases, eyegrounds normal, Wassermann negative. Blood hemoglobin, 82 per cent, red blood corpuscles, 4,800,000, white blood corpuscles, 12,000, polymorphonuclears, 56 per cent. Urine specific gravity, 1.050, albumin, boils solid, hyaline casts, no red blood corpuscles. Nephritic test day-day specimen, 748 e.c., specific gravity, 1.016-26, night specimen, 604 e.c., specific gravity, 1.022.

Course—Patient ran an up-and-down course with periods of absence of edema, although there was still some present in her ankles on discharge. February 26, tonsils were removed and at other times various decayed teeth were taken care of or extracted. January 5, had headache and vomiting lasting for two days. January 14, headache, chill, fever, pain in chest, red throat, but lungs were negative. February 19, some diarrhea. March 24, hemoglobin, 40 per cent, red blood corpuscles, 3,400,000, blood pressure as follows: December 11, 130/88, December 31, 146/106, January 16, 138/92, January 25, 122/82, Feb-

ruary 7, 148/108, February 20, 120/90, March 15, 130/90, April 12, 116/90, May 22, 108/70 Urine specific gravity varied from 1 012-27, always considerable albumin and numerous hyaline and granular casts, frequently red blood corpuscles, but none on discharge, May 22 January 14 and 15, fever of 103 F, January 23 and February 17, temperature 100 6 F

Readmission June 29 Still weak and somewhat dyspneic on exertion, ankles edematous, heart 3 by 11 cm, blood pressure, 106/68 Blood hemoglobin, 65 per cent, red blood corpuscles, 4,410,000, white blood corpuscles, 9,000 Urine specific gravity, 1 014, albumin, trace, no casts, occasional red blood corpuscles Phenolsulphonaphthalein, 50 per cent, Ambard, 50, blood urea, 0 28 gm per liter, actual plasma NaCl, 6 28 gm per liter, calculated plasma NaCl, 5 86 gm per liter, threshold, 6 04 gm per liter

Dispensary notes August 3, occasional headaches, slight edema of the legs, no nocturia, blood pressure, 110/70 Urine 1 022, faint trace of albumin, no casts September 7, feels fine, no edema or dyspnea Urine 1 029, albumin, faint trace, no casts October 19, edema of legs Urine 1 030, albumin, faint trace, no casts

Readmitted, Nov 27, 1917 No nocturia, edema of ankles every night, had been on as complete a salt-free diet as is possible outside the hospital, had been unable to go back to work, some dyspnea on exertion, had been having attacks of dyspnea without apparent cause every day for the previous two months, no asthmatic symptoms, no sense of oppression over chest Physical examination showed good color, slight edema of ankles, heart, 2 5 cm to right in fourth interspace and 10 5 cm to left in fifth interspace, blood pressure, 115/85, lungs clear Urine specific gravity, 1 015-30, albumin, trace, microscopic examination, negative, NaCl, 0 54 per cent to 0 17 per cent, daily output, 3 5 to 2 6 gm Blood hemoglobin, 80 per cent, red blood corpuscles, 4,304,000, white blood corpuscles, 6,600 Ambard, 87, phenolsulphonaphthalein, 65 per cent, blood urea, 0 21 gm per liter Actual plasma chlorid, 6 50 gm per liter, calculated plasma chlorid, 5 90 gm per liter, threshold, 6 21 gm per liter

March, 1918—Patient feels much better No edema, much less weakness

CASE 8—No 33338 Boy, aged 17, admitted Dec 2, 1916 Complaint, swelling of body Family history negative

Personal History—Never robust, at three years he began to have headaches, which at about 11 years increased in frequency for three or four years, recently they had come about every five weeks, the last one five weeks before admission, these headaches began in the morning and lasted all day, patient's mother said that at 3 years of age he had swelling of the feet that prevented his walking, his father said that one year previous he had swelling of the legs and was in bed for two weeks, after which it disappeared, not to return until the present illness

Present Illness—Onset November 6, with cold, sore throat, pains all over body, headache, fever and vomiting, went to bed and in about two days the feet began to swell and abdomen, face and hands, at the same time he passed small amounts of bloody urine, with the appearance of edema the headache and vomiting disappeared, for a week before admission the diet was restricted to milk, eggs, soups, bread and butter, on admission the patient said he felt fine

Physical Examination—Marked general edema, fluid in both chests and abdomen, tonsils moderately large, but apparently not inflamed, no hair on face or chest, transverse pubescence, skin very soft, heart 12 cm to left in fifth interspace, eyegrounds normal, Wassermann negative, urine culture showed a nonhemolytic streptococcus, blood pressure, 142/90 Blood hemoglobin, 95 per cent, red blood corpuscles, 4,670,000, white blood corpuscles, 20,400 Urine grossly bloody, specific gravity, 1 020, albumin, 12 per cent, large granular and red blood corpuscle casts, many red blood corpuscles and white blood corpuscles

Course—Although the patient began to lose weight from the beginning, the marked diuresis did not begin for about one month and it was almost three months before the edema had completely disappeared. January 9 there was a generalized urticaria which disappeared in about four days. February 12 hemoglobin, 50 per cent, red blood corpuscles, 3,400,000, white blood corpuscles, 10,200. March 19 tonsillectomy, recovery uneventful. Blood pressure December 4, 162/105, December 11, 138/80, Dec 20, 164/100, January 21, 206/140, February 7, 164/122, February 15, 128/90, March 6, 152/106, March 12, 126/94, March 20, 152/84. Urine specific gravity varied from 1.014 to 1.026, red blood corpuscles persisted in urine until about the middle of February.

Dispensary Note April 10, feels fine, no symptoms except nocturia, physical examination shows slight edema of ankles, blood pressure, 160/95. Urine 1,015, albumin, 0.4 per cent., no red blood corpuscles.

Readmission, April 30. Had had no edema, still had nocturia, felt fine. Physical examination good color, no edema, blood pressure, 155/90, red blood corpuscles, 4,000,000, hemoglobin, 86 per cent, white blood corpuscles, 12,000, phenolsulphonephthalein, 38 per cent, Ambard, 22, blood urea, 0.2 gm, actual plasma NaCl, 6.5 gm per liter, calculated plasma NaCl, 5.9 gm per liter, threshold, 6.2 gm per liter. Urine specific gravity, 1.022, albumin, heavy trace, hyaline and granular casts, no red blood corpuscles, salt concentration, 0.4 per cent.

Dispensary Note July 2, no edema, never felt better, blood pressure, 175/95. October 1 feels fine, no edema, blood pressure, 155/100. December 31 no gastric, intestinal or cardiac symptoms, no edema or headache, blood pressure, 180/100. Urine specific gravity, 1.011, albumin, heavy trace, hyaline and granular casts.

CLINICAL SUMMARY

The two cases (7 and 8) whose histories show that their disease has been of long duration, exhibit no special clinical characteristics, and are, therefore, grouped with the rest of the series in the clinical discussion. The average age was about 26 years, only one patient was over 35 years, Case 5, who was 46. The *past histories* of three of the six "acute" cases were absolutely negative from a renal point of view, one patient, Case 1, had dyspnea on exertion, Case 3 had nocturia for four months and the patient (5), whose history was not very reliable, said that he had had nocturia all his life. Searching for an etiology, we find tonsillitis in three cases, hives and rheumatic fever in one and epilepsy in another. The *present illness* varied from one to three weeks, with the onset, edema in four cases "grippe" or some acute infection in three, nocturia in one, and headache in another. Edema was marked in all except Cases 1 and 4, in which it had apparently begun to disappear before admission. Every patient but one, the fatal case, had headaches. Some acute infection, "grippe," sore throat, or cough, was present in six of the eight cases. Hematuria occurred in two cases (4 and 8), nocturia in four cases, and oliguria in two. Lumbar pain was found in only one case. There was a history of dyspnea on exertion in three cases, all acute. The only constant feature, therefore, was edema, with headaches in every case but one. The other symptoms occurred quite accidentally, distributed indifferently between the acute and chronic cases.

On *physical examination* there was general edema in six cases and slight dependent edema in the other two (1 and 4), the blood pressure was above normal in all the cases, ranging from 136/86 mm to 180/150 mm, but in every instance it returned to normal while in the hospital, rising again after discharge in Cases 5 and 8 only. The heart was normal in size in Case 3, slightly enlarged in Cases 2, 4, 7 and 8, moderately enlarged in Cases 1 and 6, and considerably enlarged in Case 5. It is worthy of mention that in the latter three cases the systolic blood pressure was over 174 mm, whereas the next highest pressure was 154 mm, in other words, an apparent relation between the degree of hypertension and cardiac hypertrophy. Pyorrhea was found in six cases, tonsillar abnormality in four cases, while Cases 3 and 8 showed no foci of infection. Leukocytosis (over 10,000) was present in six cases, occurring in the two cases that showed no infection at the onset. There was, during the hospital stay, definite anemia in every case, and all except Cases 1 and 3 showed red blood cells in it. No constant relationship between the amount of hematuria and the degree of anemia could be demonstrated. There were no other significant physical findings. Albuminuria in varying amounts was found in every case, and all except Cases 1 and 3 showed red blood cells in the urine, while two cases (4 and 8) were grossly hematuric. The four cases with only a trace of albumin on admission had the most favorable courses, but the influence of the total output of urine on the concentration of albumin, as shown by a simple qualitative test, will help to explain this observation. Every case had hyaline casts, and the grossly hematuric cases had red blood cell casts.

From the history and clinical examination one cannot separate these cases into definite categories. Edema, hypertension, albumin and casts were constant, but other details were quite promiscuously distributed, for example, the two cases with gross hematuria were otherwise quite unlike, and the case with the highest blood pressure showed among the fewest abnormalities. There is, however, a single exception in Cases 5 and 6, for they show similar histories and the clinical findings correspond rather closely, but if we compare their courses we see that one patient died while the other improved most remarkably. It seems, therefore, that a clinical classification of this series is quite impossible.

The course in each case is summarized in the case history, but there are certain points that are worth noting. During the hospital stay three of the acute cases made a complete symptomatic recovery, two improved greatly and one died, of the chronic cases, one improved very much, and the other hardly at all. The discharge physical examination showed only one case (7) with edema, and none with hypertension, but the anemia in each instance persisted. Those patients who

TABLE 1—DATA IN CASE 1*

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul- phone phthal ein	Urea Index				Chlorid Index †				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
March 7- 8	134 0	1,500	446	2 0	1 9	38	0 1	7 8	5 7	535	5 8	4 3	5 94	5 82	5 74
8- 9	130 8	1,500	900	2 0	4 0										
9 10	137 5	1,500	1,500	2 0	6 9										
10 11	128 5	2,000	1,050	0 6	1 9										
11-12		2,000	1,335	0 8	0 5										
12-13	129 5	1,500	2,000	0 8	0 6										
13 14	128,5	1,500	1,550	0 8	0 5										
14-15	128 5	1,500	300+	0 8	0 4										
15 16	129 0	1,500	1,070	0 8	0 5										
16 17	128 0	1,500	1,130	0 8	1 2	48	0 22	7 0	17 5	141	3 1	7 8	5 80	5 85	5 57
17 18	127 5	1,500	1,605	0 8	1 2										
18 19	127 0	1,500	1,670	0 8	1 3										
19 20	127 0	1,500	1,418	7 8	1 5						0 4	0 7	5 89	5 62+	5 89†
20 21	128 0	1,500	1,430	0 8	2 9						0 4	1 1	5 96	5 62+	5 96§
21 22	128 0	1,200	710	0 8	1 4						1 5	2 9	6 14	5 74	6 02¶
22 23	127 5	1,500	1,000	0 8	2 1										
23 24	128 0	1,500	1,190	0 8	1 4										
24 25	127 5	1,500	1,300	0 7	1 4										
25 26	127 5	1,500	1,450	0 8	2 7										
26 27	127 0	1,500	1,180	0 7	0 9										
27 28	127 5	1,500	1,950	0 7	1 5										
28-29	128 0	1,500	1,440	0 7	0 6										
29 30	127 5	1,500	1,270	0 7	0 5										
30 31	128 0	1,500	1,510	3 2	1 4										
31 Apr 1	127 0	1,500	1,472	3 2	2 8	65	0 18	5 1	13 6	140	2 5	6 7	5 94	5 82	5 74
1- 2	127 0	1,500	630	3 2	0 8										
2 3	128 0	1,500	1,400	3 2	3 3										
3 4	127 0	1,800	2,120	3 2	3 9										
4- 5	127 0	1,800	1,330	3 2	1 9										
5 6	125 6	1,800	1,410	3 1	2 9										
6 7	126 5	1,800	2,150	3 1	4 1										
7 8	127 0	1,800	1,830	3 1	3 5										
8 9		1,800	2,370	3 1	3 6										
9 10	128 5	1,800	1,730	3 2	3 9										
10-11	128 0	1,800	2,280	3 2	4 8										
11 12	128 5	1,560	2,356		5 0	64	0 19	2 5	11 6	75	2 7	12 43	6 03	5 90	5 74
June 20						60	0 20	2 8	18 1	111	2 3	20 5	6 01	5 97	5 67

* Fluids expressed in cc, urinary chlorids in gm, blood concentration in gm per liter

† Weight for index = 61 kg

‡ At 1 30 p m, 7 gm NaCl at 2 p m

§ At 3 30 p m

¶ At 1 20 p m

TABLE 2—DATA IN CASE 2

ate	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul phone phthal ein	Urea Index				Chlorid Index *				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thre old
1	158 5	1,500	1,170	2 4	12 9	44	0 88	20 0	22 5	98	3 9	4 3	6 33	5 79	6 1
2	154 0	1,500	2,450	2 4	16 5										
3	149 0	1,500	2,480	2 4	14 9										
4	144 5	1,500	1,696	2 4	9 6	53	0 31	12 1	18 4	94	7 7	19 6	5 99	6 07	5 5
5	141 5	1,500	2,065	2 4	8 4										
6	137 5	1,500	2,060	2 4	10 6										
7	133 0	1,480	2,120	0 5	5 1										
8	130 5	1,500	1,940	0 5	4 0										
9	130 5	1,500	1,330	0 3	2 9										
10	129 5	1,500	1,410	0 6	3 2										
11	129 5	1,500	1,000	0 7	2 5										
12	128 5	1,500	920	0 7	2 0										
13	129 0	1,500	1,540	0 6	2 3										
14	127 5	1,500	1,250	0 7	0 8										
15	128 0	1,500	895	0 7	0 8	48	0 37	9 2	22 4	70	1 4	3 5	5 78	5 74	5 65
16	127 5	1,500	636	7 7	0 8						0 42	0 6	5 84	5 62+	5 84-
17	128 5	1,500	1,080	0 7	2 1						0 82	0 68	6 03	5 62+	6 03-
18	128 5	1,450	1,158	3 8	3 2						2 3	4 3	6 00	5 73	5 84
19	128 0	1,450	960	3 8	4 2										
20	129 0	1,500	1,060	3 8	5 1										
21	128 0	1,450	750	3 7	4 2										
22	128 0	1,500	735	3 7	6 1										
23	131 3	1,500	1,280	3 5	3 4										
24	129 5	1,500	810	3 7	1 6										
25	130 0	1,500	1,010	3 7	3 0										
26	130 0	1,500	1,980	3 8	2 9										
27	130 0	1,500	1,040	3 8	5 8										
28	127 0	1,500	1,200	3 5	5 7	51	0 23	6 0	18 1	118	3 3	10 6	5 90	5 88	5 60
29	130 0	1,500	1,270	3 7	4 1										
30	130 0	1,500	880	3 6	3 9										
31	131 5	1,500	1,130	3 4	3 5										
pr 1	130 5	1,500	1,600	3 4	6 4										
2	131 0	1,500	950	3 6	6 0										
3	133 0	1 500	1,220	3 5	6 4										
4	130 5	1,500	1,410	3 5	3 9										
5	129 5	1,500	880	4 4	5 2										
6	129 5	1,500	600	4 6	2 5										
7	130 3	1,500	1,760	4 6	8 4										

* Weight for index = 63 7 kg

† At 1 30 p m 7 gm NaCl at 2 p m

‡ At 3 30 p m

TABLE 2—DATA IN CASE 2—(Continued)

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul phone phthal cin	Urea Index				Chlorid Index				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
April 7- 8	131 3	1,500	945	4 5	5 5										
8 9	133 0	1,500	955	4 6	6 2										
9 10	130 5	1,500	1,547	4 4	6 5	60	0 2	4 1	16 4	116	2 5	13 6	5 89	5 93	5 58
10 11	130 5	1,500	570	4 4	1 9										
11-12	130 5	1,500	660	4 6	2 0										
12 13	132 0	1,500	1,410	4 6	4 1										
13 14	134 0	1,500	1,750	4 6	5 0										
14 15	132 5	1,500	1,140	4 6	4 0										
15-16	133 0	1,500	1,300	4 6	2 8										
16 17	132 0	1,500	1,940	4 6	7 3										
17 18	133 0	1,500	1,350	4 6	1 6										
18 19	135 5	1,800	1,913	4 4	4 5										
19 20	132 5	1,800	1,080	4 6	4 6										
20 21	135 0	1,700	1,500	4 6	2 7										
21 22	134 5	1,800	1,300	4 6	3 7										
22 23	135 0	1,700	1,410	4 6	5 6										
23 24			858		4 3	58	0 27	9 1	16 2	95	4 9	8 8	6 06	5 89	5 79
May 31					.		0 15	17 3	20 4	531	15 0	17 6	6 25	6 12	5 75

§ Uncontrolled

TABLE 3—DATA IN CASE 3*

Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul- phone phthal- ein	Urea Index				Chlorid Index †				
	In	Out	In	Out		Blood Urea	O	D	Index	O	D	Plasma NaCl	Calcul Plasma NaCl	Thresh eld
184 5			0 32											
180 0	530	2,905+	0 32	19 7+	65	0 27	6 7	16 5	73	9 5	23 3	6 40	6 10	5 92
173 0	775	4,430	0 43	28 4										
163 0	1,080	2,925	0 43	15 7						6 7	19 0	6 46	6 02	6 06
157 5	1,200	2,350	0 43	9 8										
153 5	1,200	2,524	0 43	8 4						3 0	8 8	6 35	5 84	6 13
150 5	1,200	2,135	0 43	8 4										
148 5	1,200	1,430	0 43	4 9										
146 5	1,200	1,720	0 43	3 9										
146 0	1,200	1,790	0 43	3 1										
144 0	1,500	1,390	0 43	2 1	42	0 45	3 5	11 4	13	1 3	4 2	6 24	5 75	6 11
143 5	1,200	1,520	0 60	2 0										
143 5	1,200	1,525	0 60	3 7										
143 5	1,200	1,620	0 60	1 8										
144 5	1,200	1,960	0 60	1 2										
143 5	1,200	1,705	0 60	1 2										
143 0	1,200	1,880	0 60	1 1										
142 5	1,200	1,150	0 60	0 6										
141 5	1,200	1,074+	0 40	lost	35	0 71	6 0	15 0	9	0 6	1 53	6 25	5 62+	6 25—
141 5	1,200	915	0 6	0 5										
142 0	1,200	1,580	0 6	0 6										
142 5	1,200	1,615	0 6	0 6										
141 5	1,200	1,590	0 6	0 9										
142 0	1,200	1,565	0 6	0 6										
140 3	1,200	1,940	0 6	1 0										
141 5	1,200	1,505	0 6	1 1										
139 7	1,200	1,310	0 6	1 3	42	0 25	4 3	10 9	45	0 9	2 1	6 13	5 62+	6 13—
140 5	1,200	970	0 6	1 1										
140 5	1,200	1,100	3 6	1 5										
141 5	1,200	870	3 6	1 3										
142 0	1,400	965	3 6	2 7										
142 5	1,200	1,360	3 6	3 3										
142 5	1,200	1,200	3 6	4 3										
141 5	1,200	1,350	3 6	4 8	41	0 19	4 4	16 5	133	2 2	9 2	6 15	5 83	5 94
142 5	1,200	1,440	3 6	5 3										
142 5		1,060	3 6	5 3										
143 0		1,305	3 6	3 0										
142 3	1,200	960	3 6	4 5										

The diet for the period May 4 to May 15 contained 1300 calories and a nitrogen content of 5 gm, from May 16 to May 30, 2,000 calories and 5 gm nitrogen, from May 31 to June 25, 2,500 calories and 6 gm nitrogen, from June 26 to June 30, 2,500 calories and a nitrogen content of 12 gm.

Weight for index = 72.7 kg

TABLE 3—DATA IN CASE 3*—(Continued)

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul- phone phthal- ein	Urea Index				Chlorid Index				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
June 11-12	142 0	1,200	970	8 6	5 4										
12-13	142 5	1,200	1,110	8 6	5 8										
13-14	143 5	1,200	1,215	8 6	9 7										
14-15	142 7	1,200	1,528	8 6	7 5	54	0 30	2 8	14 5	34	2 8	14 4	6 19§	5 90	5 91§
15-16	144 3	1,800	2,310	8 6	9 6										
16-17	143 5	1,800	2,010	8 6	9 6										
17-18	144 5	1,800	1,800	8 6	7 2										
18-19	144 5	1,760	1,357	8 6	7 3										
19-20	144 3	1,800	610	8 6	7 5										
20-21	144 7	1,800	1,150	8 6	8 7										
21-22	143 7	1,800	1,182	8 6	6 3	55	0 29	9 4	7 0	32	10 3	7 7	6 35	5 90	6 07
22-23	144 5	1,800	700	8 6	8 5										
23-24	144 7	1,800	795	8 6	12 2										
24-25	144 7	1,800	870	8 6	9 5										
25-26	144 7	1,800	1,990	8 8	17 9										
26-27	144 3	1,800	1,120	8 8	8 0										
27-28	144 0	1,800	1,180	8 8	10 0										
28-29	144 5	1,800	1,670	8 8	11 5										
29-30	144 0	1,800	1,620	8 8	11 2										
30-July 1	143 3	1,800	1,100	8 8	7 3										
1-2	143 4	1,800	1,730	8 8	11 2										
2-3	142 0	1,800	1,100	8 8	7 2	30	0 49	17 0	15 3	33	12 0	10 8	6 25	5 97	5 90
3-4	140 0	1,800	1,705	4 8	8 1										
4-5		1,800	1,600	4 8	5 8										
5-6		1,800	1,480	4 8											
6-7		1,800	1,100	4 8	2 5										
7-8		1,800	1,550	4 8	2 3										
8-9		1,800	1,940		3 7										
9-10		1,800	1,520		3 0										
10-11		1,800													
11-12		1,800	1,980												
12						50	0 28	1 68	13 4	27	1 9	15 5	6 06§		
Jan 1, '18							0 20	2 0	14 9	65	2 1	15 6	6 60§	5 89	6 33

§ Uncontrolled

TABLE 4—DATA IN CASE 4

No.	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul- phone phthal- ein	Urea Index				Chlorid Index *				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thre old
20	102 0	2,000	1,840	2 0	3 3										
21	100 0	1,500	1,572	2 0	3 2	26	0 27	2 8	6 0	27	1 7	3 6	6 11	5 78	5 98
22		1,500	1,600	2 0	4 0										
23	97 5	1,700	1,320	?	3 6										
24		1,700	1,670	?	4 8										
25	95 0	1,700	1,710	?	3 4										
26		1,800	1,060	3 0	1 7										
27	96 0	1,800	1,520	3 0	1 9										
28		1,800	1,350	3 0	2 2										
29		1,800	1,330	3 1	2 4										
30	94 5	1,800	1,600	3 1	3 2										
31	94 0	1,800	1,692	3 1	3 5	37	0 67	7 0	15 2	18	2 2	4 8	5 92	5 81	5 73
32	93 0	1,800	1,350	3 1	2 6										
33	92 5	1,800	1,410	3 1	2 6										
34	93 5	1,600	1,360	2 7	2 1										
35	93 0	2,000	1,500	1 3	2 5										
36	93 0	2,000	1,820	0 46	1 8										
37	92 0	2,000	1 650	0 46	1 5										
38	90 5	1,600	1,720	0 45	1 2										
39	90 5	1,600	1,165	0 45	0 8										
40	90 5	1,600	1,440	0 26	1 4	21	0 71	7 2	6 8	7	0 7	0 6	6 03	5 62	6 02
41	89 5	1,600	1,179	0 2	0 7										
42	89 5	1,600	1,530	0 45	0 7										
43	89 0	1,600	1,260	0 46	0 8										
44	90 0	1,600	1,440	0 26	0 7										
45	89 0	1,600	1,950	0 26	4 3										
46	88 0	1,600	1,216	0 26	0 6						0 5	0 6	5 75	5 62	5 74
47	88 0	1,600	1,180	0 26	0 5										
48	88 0	1,600	910	0 46	0 4										
49	86 5	1,600	1,050	0 26	0 4										
50	86 5	1,480	1,010	0 22	0 5										
51	86 5	1,600	980	0 22	0 3										
52	86 0	1,600	1,060	0 22	0 4										
53	86 0	1,600	1,180	0 22	0 7										
54	86 0	1,600	850	0 22	0 3										
55	84 5	1,600	1,020	0 22	0 4										
56	85 0	1,600	987	0 22	0 4	15	0 96	8 2	7 6	5	0 5	0 4	5 75	5 62	5 74
57	86 0	1,600	1,220	0 643	0 3										

* Weight for index = 45.5 kg

TABLE 4—DATA IN CASE 4—(Continued)

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul- phone phthal- ein	Urea Index				Chlorid Index				Thresh- old
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	
March 29-30	80.0	1,600	1,500	2.14	0.5										
30-31	87.0	1,600	1,180	2.12	0.6										
31-Apr 1	87.5	1,600	1,440	2.14	0.7										
1- 2	88.2	1,600	1,240	2.14	0.8										
2- 3	88.0	1,600	1,110	2.09	0.9										
3- 4	86.5	1,600	1,550	2.09	1.4										
4- 5	86.5	1,600	1,240	2.09	1.3										
5- 6	86.5	1,600	1,220	2.09	1.8										
6- 7	88.0	1,600	1,340	2.09	1.9	44	0.26	3.1	4.1	22	1.7	2.2	5.93	5.74	5.81
7- 8	87.0	1,600	1,360	2.09	2.0										
8- 9	87.0	1,600	1,130	2.00	1.7										
9-10	88.0	1,600	1,410	2.09	2.2										
10-11	88.5	1,600	1,550	2.09	2.2										
11-12	89.5	1,600	1,680	2.09	2.9										
12-13	89.0	1,600	1,170	2.09	2.0										
13-14	89.0	1,600	1,210	2.09	2.1										
14-15	90.0	1,600	1,350	2.09	1.9										
15-16	90.5	1,500	1,150	2.09	2.2										
16-17	88.0	1,600	1,300	2.09	2.4										
17-18	87.5	1,600	1,411	0.5	2.6	30	0.22	1.8	4.7	26	2.0	5.3	5.94	5.82	5.74
18-19	89.5	1,600	1,150	2.09	1.4										
19-20	89.0	1,760	1,327	2.09	2.6										
20-21	90.0	1,600	1,280	2.09	1.8										
21-22	89.5	1,600	1,700	2.09	2.0										
22-23	90.8	1,600	1,450	2.09	2.0										
23-24	91.0	1,500	1,610	2.09	2.7										
24-25	90.5	1,600	1,370	2.09	2.3										
25-26	92.0	1,600	1,210	2.09	2.5										
26-27	90.5	1,600	1,650	2.09	3.4										
27-28	89.5	1,600	750	2.09	1.6										
28-29	90.0	1,600	1,750	2.09	3.6										
29-30	89.5	1,400	1,370	2.09	3.9										
30-May 1	90.5	1,500	1,450	2.09	2.9										
1- 2	92.0	1,600	1,150	2.09	2.2										
2- 3		1,300	1,150	2.09	2.5										
3- 4	89.5	1,600	956	2.09	2.6	37	0.16	2.6	4.6	58	2.0	3.5	6.00	5.78	5.84
4- 5	90.5	1,600	770	2.09	1.8										
5- 6		1,300	1,270	2.09	2.6										

TABLE 4—DATA IN CASE 4—(Continued)

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul phone phthal ein	Urea Index				Chlorid Index				
		In	Out	In	Out		Blood Urea	O	D	Index	O	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
May 6 7	89 5	900	1,140	2 09	2 6										
7 8		1,000	1,330	2 09	2 9										
8 9	91 0	900	1,110	2 09	2 5										
9 10	92 0	1,100	580	2 09	1 7										
10-11	92 0	1,100	850	2 09	1 7										
11 12	92 5	1,000	1,180	2 09	2 6										
12 13	92 5	1,300	1,140	2 09	2 9										
13 14	91 5	1,000	1,340	2 09	4 0										
14 15	92 0	1,000	1,150	2 09	2 5										
15-16	93 0	900	1,070	2 09	2 3										
16 17	92 0	1,100	961	2 09	2 2	42	0 18	3 8	4 2	50	3 0	3 3	5 93	5 79	5 70
17 18 Nov 12, 1917	92 5	1,000	1,230	2 09	2 8	67	0 26	3 0	15 6	79					

TABLE 5—DATA IN CASE 5

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul phone phthal ein	Urea Index				Chlorid Index *				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thi olu
May 15 16	139 0	1,200	292		0 3	15	1 41	11 9	1 0	1	1 2	0 4	6 59	5 62	6 55
16 17	138 5	1,065	735	0 5	0 7										
17 18	137 5	1,200	1,125	0 5	1 2										
18 19	134 5	1,200	810	0 5	0 9										
19 20	133 5	1,200	1,215	0 5	2 1										
20-21	129 0	1,200	1,505	0 5	3 0										
21 22	129 0	1,200	1,225	0 4	3 3										
22 23	128 5	1,200	1,520	0 4	4 3										
23 24	125 5	1,200	1,312	0 4											
24 25	123 5	1,200	1,460	0 4	5 3										
25-26	122 5	1,200	1,630	0 5	6 6	25	0 75	12 2	17 1	15			6 30		
26-27	122 5	1,200	1,180	0 76	4 0										
27 28	120 0	1,200	1,200	1 2	3 5										
28 29	121 0	1,200	1,030	1 2	3 1										
29 30	120 5	1,200	870	1 04	2 2										
30 31	120 0	1,200	365	1 04	1 4										
31 June 1	118 5	1,200	1,391	1 03	5 2	26	0 32	7 8	4 7	18	3 1	1 8	5 94	5 73	5 8
1- 2	118 0	1,200	1,650	1 03	5 0										
2 3	116 0	1,200	1,880	1 03	6 4										
3 4	115 5	1,200	1,620	1 03	5 2										
4- 5	112 5	1,200	1,660	1 03	3 2										
5- 6	111 5	1,200	1,900	1 03	6 1										
6- 7	109 0	1,200	1,900	1 03	2 9										
7 8	108 0	1,200	1,860	1 03	4 8										
8 9	108 0	1,200	1,250	1 03	4 4										
9 10	106 5	1,200	1,250	1 03	2 8										
10-11	105 3	1,200	1,650	1 03	4 6										
11 12	104 0	1,200	1,570	1 03	3 9	19	0 32	4 3	3 2	9	1 0	0 7	5 91	5 62	5

* Weight used for index = 63 kg

TABLE 6—DATA IN CASE 6

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul phone phthal ein	Urea Index				Chlorid Index *				
		In	Out	In	Out		Blood Urea	C	D	Index	O	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
Feb 26 27	123 5	1,500	690	0 37	1 6	20	1 56	6 8	3 9	0 5	1 1	0 6	6 13		
27 28	124 0	1,500	610	2 4	0 8										
28-Mar 1	124 0	1,500	350 ?	2 4	0 8										
1 2	123 5	1,500	544	2 4	0 5						0 9	0 4	6 19		
2 3	123 5	1,500	730	0 52	0 7										
3 4	125 0	1,500	440	0 28	0 3										
4 5		1,500	535	0 52	0 2										
5 6	125 0	1,500	770	0 52	0 4										
6 7		1,360	350	0 52	0 1										
7 8	125 5	1,500	400	0 52	0 2										
8 9	126 5	1,500	630	0 52	0 2										
9 10	127 5	1,500	475	0 4	0 2	14	2 11	8 0	5 7	0 6	0 3	0 2	5 99		
10-11	127 0	1,500	630	0 52	0 2										
11 12	128 0	1,500	290	0 52	0 1										
12 13	128 8	1,300	355	0 5	0 1										
13 14	127 5	1,250	700	0 5	0 2										
14 15	131 0	1,500	355	0 5	0 1										
15 16	129 5	1,000	500	0 5	0 2										
16 17	127 5	1,000	600	0 5	0 2										
17 18	128 0	1,000	520	0 65	0 4										
18 19	128 5	2,000	640	2 5	0 2										
19 20	129 5	2,000	780	2 4	0 3										
20 21	130 5	1,710	490	1 9	0 1	6	2 15	7 7	3 7	0 4	0 3	0 2	5 38		
21 22	131 0	1,800	465	2 12	0 2										
22 23	130 0	1,790	680	2 50	0 2										
23 24	131 5	2,050	500	2 62	0 2										
24 25	131 0	2,000	766	2 40	0 2						0 3		5 20		
25 26	132 5	1,910	550	2 52	0 2										
26 27	136 5	2,000	620	2 52	0 2										
27 28	137 5	1,400	260	0 97	0 1		2 95						4 53†		
28-29	136 5	1,500	790	1 34	0 1										
29 30	136 0	1,800	750	2 04	0 1										
30 31		1,750	775	1 76	0 1										
Apr 1	137 0	1,850	680	2 15	0 1										
1- 2		1,800	720	2 21	0 1										
2 3	138 0	1,600	630	1 52	0 1										
3 4		1,750	810	2 48	0 2										
4- 5		1,400	640	1 68	0 1										

* Weight used for index = 56.1 kg

† NaCl in chest fluid = 4.88 gm per liter

TABLE 6—DATA IN CASE 6—(Continued)

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul- phone- phthal ein	Urea Index				Chlorid Index				T old
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	
April 5-6	140.0	1,925	490	2.45	0.1		3.30						4.45		
6-7		2,000	620	2.58	0.1										
7-8	139.0	1,600	370	2.07	0.1										
8-9		1,500	630	2.48	0.3										
9-10		1,250	430	1.43	0.1										
10-11	139.3	1,400	515	1.39	0.2										
11-12	138.0	1,225	420	0.39	0.2										
12-13		1,500	370	0.25	1.1										
13-14		1,425	410	0.40	0.2										
14-15	138.5	1,330	250 ⁺	0.40	0.1										
15-16		440	240	0.40	0.1										
16-17		1,100	260	0.40	0.2		4.36	4.5	0.4				4.56		
17-18		1,100	230	0.40	0.2										
18-19		675	170	0.20	0.1										
19-20		1,000	100	0.40	0.1										
20-21			325		0.20		4.59						4.45 [‡]		

[‡] April 21 Tissue juices at operation 4.69 gm per liter of NaCl

TABLE 7—DATA IN CASE 7

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul- phone phthal- ein	Urea Index				Chlorid Index *				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
Dec 4 5	157 0	1,000	400		2 6										
5 6		1,900	1,100	3 0	5 1	58	0 19	5 6	19 0	155	2 3	7 9	6 26	5 82	6 06
6 7		1,500	1,820	3 0	10 6										
7 8	152 0	2,000	2,540	3 0	11 2										
8 9	148 9	2,000	1,700	3 0	7 9										
9 10	146 7	2,000	2,050	3 0	6 4										
10-11		2,000	2,500	3 0	8 0										
11 12	143 4	2,000	1,760	1 0	5 4										
12 13	143 2	2,000	1,620	1 0	3 2										
13 14	143 0	2,000	1,645	1 0	3 3		0 14	3 0	12 3	135					
14-15	142 3	2,000	2,200	1 0	4 0										
15-16	141 7	2 000	2,000	1 0	4 7										
16 17	141 9	2,000	1,705	1 0	4 6										
17 18		2,000	1,710	1 0	4 1										
18 19	141 9	2,000	2,060	1 0	4 7										
19 20	141 7	2,000	1,540	1 0	2 4										
20-21		2,000	1,356	1 0	2 4	44	0 13	1 9	4 8	52	2 6	6 7	6 31	5 81	6 22
21 22	144 8	2,000	1,406	1 0	3 4										
22 23	143 0	2,000	950	1 0	2 0										
23 24	143 2	2,000	1,240	1 0	1 4										
24 25		2,000	1,260	1 0	0 9										
25 26		2,000	1,720	1 0	1 3										
26 27	144 9	2,000	1,240	1 0	1 5										
27 28	146 3	2,000	1,755	1 0	3 0										
28 29	148 1	2,000	1,500	1 0	2 0										
29 30	148 1	2,000	1,120	1 0	1 5										
30-31	149 6	2,000	1,300	1 0	1 6										
31 Jan 1		2,000	1,390	1 0	2 0										
1 2		1,600	1,440	1 0	1 8										
2 3	151 4	2,000	1,170	1 0	1 2										
3-4		2,000	1,708	1 0	3 0	40	0 24	3 5	9 5	39	2 1	5 7	6 45	5 78	6 29
4 5	152 9	2,000	1,020	6 0	2 9										
5 6	150 5	600	910	6 0	6 2										
6 7	151 8	970	750	6 0	5 8										
7 8	151 8	1,200	755	6 0	6 0										
8 9	155 3	2,000	890	6 0	3 8										
9 10	155 3	2,000	1,050	6 0	3 2										
10 11	155 3	2,000	1,545	6 0	4 1										
11 12	155 3	2,000	870	6 0	3 4										

* Weight used for index = 718 kg

TABLE 7—DATA IN CASE 7—(Continued)

Date	Weight, Lbs	Fluid Exchange		Ohlorid Exchange		Phenol-sul phone-phthal ein	Uren Index				Chlorid Index				Thres old
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	
Jan 12 13	155 9	2,000	1,110	6 0	5 5										
13 14	157 9	2,000	1,500	1 8	7 8										
14 15		1,200	1,960	1 0	5 2										
15-16	152 4	800	1,040	0 0	4 3										
16 17		1,050	675	1 2	0 2										
17 18		1,200	445	1 3	0 2										
18 19	151 1	1,450	813	1 5	0 4	71	0 14	10 0	10 0	200	0 9	0 9	5 9S	5 62	5 9,
19 20		1,500	1,160	1 5	0 5										
20-21	153 1	1,680	1,165	1 2	0 5										
21 22		1,450	910	1 8	0 5										
22 23	154 2	1,430	690	1 9	0 3										
23 24		1,200	740	1 2	0 4										
24 25		850	360	1 0	0 2										
25 26		1,600	510	1 6	0 2										
26 27	154 0	1,400	760	1 6	0 2										
27 28	153 3	1,500	620	1 6	0 2										
28 29		1,200	820	1 6	0 2										
29 30	153 1	1,200	640	1 6	0 2										
30 31	152 6	1,200	660	1 0	0 2										
31 Feb 1	153 1	1,200	1,200	1 0	0 3										
1- 2	152 2	1,200	720	1 0	0 6										
2 3		1,200	840	1 0	1 1										
3 4	152 7	1,200	775	1 0	1 1	48	0 12	2 7	6 9	97	1 1	2 8	6 08	5 72	5 9
4 5		1,200	810	1 0	0 8										
5 6	152 7	1,200	740	1 0	1 5										
6 7		1,200	1,210	1 0	1 7										
7 8	153 3	1,200	660	1 0	1 3										
8 9	154 0	1,200	615	1 0	0 7										
9 10	153 6	1,200	1,000	1 0	1 7										
10 11	153 6	1,200	950	1 0	3 7										
11 12		1,200	1,090	1 0	5 9										
12 13		1,200	960	1 0	3 7										
13 14	151 5	1,200	1,310	1 0	3 7	55	0 14	2 2	6 3	59	2 0	5 9	6 00	5 79	5 8
14 15	150 0	1,200	1,600	1 0	6 0										
15 16	147 5	1,200	1,330	1 0	5 1										
16 17	147 5	1,200	1,860	1 0	7 2										
17 18	145 0	1,200	1,340	1 0											
18 19	143 5	1,200	470	1 0	1 6										

TABLE 7—DATA IN CASE 7—(Continued)

[illegible]

TABLE 7—DATA IN CASE 7—(Continued)

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul- phone phthal- ein	Urea Index				Chlorid Index				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
March 29 30	151 5	1,200	710	14	34										
30 31	150 5	1,200	800	11	37										
30-Apr 1		1,200	900	11	52										
1- 2	149 0	1,200	930	12	46										
2 3	147 5	1,200	920	09	54										
3- 4	146 0	1,200	1,650	08	53	55	0 21	3 5	10 3	55	3 1	9 0	5 89	5 85	5 66
4- 5	144 0	1,200	1,900	08	83										
5- 6	142 0	1,200	1,100	13	29										
6 7	140 0	1,200	1,000	13	36										
7- 8	139 0	1,200	1,430	16	41										
8 9	138 5	1,200	1,050	16	27										
9 10	138 5	1,200	1,000	16	30										
10-11	138 5	1,200	900	16	18										
11 12	139 0	1,200	760	16	13										
12 13	140 0	1,400	600	18	13										
13 14	141 0	1,350	1,020	17	13										
14 15	141 5	1,350	994	19	14	24	0 17§	2 3§	6 6§	43§	0 8	2 3	6 03		
15 16	140 5	1,350	590	18	12										
16 17	142 0	1,350	720		15										
17-18	142 5	1,350	1,220	10	37										
18-19	141 0	1,350	1,120	10	11										
19 20	141 5	1,350	1,890	10	13		0 39	5 7	22 2	43	0 7	2 8	6 00		
20-21	141 0	1,350	1,120	10	07										
21-22	142 5	1,350	1,380	10	07										
22 23	140 5	1,350	1,450	10	23										
23 24	140 5	1,350	910	10	06										
24 25		1,350	1,450	10	05										
25-26	140 0	1,350	1,720	10	11										
26-27	140 0	1,350	1,290	10	18										
27 28	139 0	1,400	1,401	80	35	40	0 28	5 9	21 1	81	1 9 3 6 3 8 3 5 4 1	6 7 3 9 5 2 4 1 4 8	5 94 6 24 6 34 6 33 6 16	5 79 5 78 5 70 5 78 5 80	5 77† 6 09‡ 6 16¶ 6 17# 5 98°
28 29		1,350	1,078	10	33										
29 30	140 0	1,350	1,380	09	29										
30-May 1	130 0	1,350	1,830	10	50										
1- 2	137 5	1,350	1,650	10	53										
2 3	137 0	1,760	1,432	10	16										
3- 4	137 0	1,350	1,180	10	08										
4 5	136 7	1,350	950	10											

† At 9 a m , 35 gm NaCl at 12 n , 35 gm NaCl at 1 p m

‡ At 1 p m April 27

¶ At 3 p m April 27

At 5 p m April 27

° At 12 n April 28

§ Results uncontrolled

TABLE 7—DATA IN CASE 7—(Continued)

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul phone phthal ein	Urea Index				Chlorid Index				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
May 5-6	135.5	1,350	1,080	10	08	.									
6-7		1,350	830	10	05										
7-8	136.5	1,350	730	10	04										
8-9	136.5	1,350	730	40	04										
9-10	137.5	1,360	720	40	06										
10-11	138.0	1,350	840	40	04										
11-12	139.5	1,350	700	40	10										
12-13	140.5	1,350	1,380	40	02										
13-14	141.0	1,350	715	40	21										
14-15	141.0	1,350	770	40	21										
15-16	142.0	1,350	1,236	40	23	52	0.34	8.8	21.8	70	1.5	3.7	6.24	5.74	6.12
16-17	143.0	1,350	870	40	24										
17-18	143.5	1,350	1,140	09	22										
18-19	143.5	1,350	1,360	06	12										
19-20	143.0	1,350	960		09										
20-21			815		07										
21-22			1,240		04										
June 26						50	0.28	3.1	15.3	43	2.2	10.8	6.29	5.85	6.05
Nov 28						65	0.21	2.4	18.0	79	2.1	15.8	6.50	5.89	6.23

TABLE 8—DATA IN CASE 8

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol- sul- phone- phthal- ein	Urea Index				Chlorid Index *				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
Dec 4-5		880	1,073		07	20	1 25	14 9	20 4	8	0 3	0 4	6 41§		
5-6	166 3	1,800	1,140	2 4	0 5										
6-7	165 0	1,800	1,140	2 4	0 6										
7-8	163 5	1,800	1,060	2 4	0 9										
8-9	163 5	1,800	1,240	2 4	1 7										
9-10	162 1	1,800	1,115	2 4	1 1										
10-11		1,800	1,100	2 4	1 1										
11-12	161 3	1,800	1,000	2 4	1 2										
12-13	161 7	1,500	920	1 1	1 3										
13-14	160 4	1,500	1,060	1 1	1 5										
14-15	159 7	1,500	950	1 1	1 7										
15-16	159 3	1,500	950	1 1	1 8										
16-17	159 0	1,500	935	1 1	1 7										
17-18		1,500	840	1 1	1 9										
18-19	158 6	1,500	640+	1 1	2 0										
19-20	158 4	1,500	870	1 1	2 0										
20-21	159 1	1,500	768	1 1	1 5										
21-22	158.8	1,500	790	1 1	1 9										
22-23		1,500	830	1 1	1 9										
23-24	159 0	1,500	1,180	1 1	2 5										
24-25		1,315	1,560	1 1	4 4										
25-26	160 0	1,500	1,125	1 1	2 4										
26-27	157 0	1,535	1,600	1 1	1 9										
27-28		1,500	1,275	1 1	2 0										
28-29	155 0	1,500	1,600	1 1	2 0										
29-30	155 0	1,500	1,225	1 1	2 2										
30-31	156 0	1,500	1,200	1 1	1 8										
31 Jan 1	155 5	1,500	1,375	1 1	2 8										
1-2	155 5	1,500	1,250	1 1	3 0										
2-3	155 5	1,460	1,300	1 1	2 2										
3-4	154 5	1,500	1,700	1 1	3 1										
4-5	154 5	1,500	1,410	1 1	3 3										
5-6	153 5	1,500	1,230	1 4	1 3										
6-7	153 5	1,500	1,600	1 4	4 8										
7-8	152 0	1,500	1,740	1 4	3 5										
8-9	151 5	1,500	1,480	1 4	3 4										
9-10	149 5	1,500	1,360	1 4	2 7										

* Weight used for index = 58 kg

§ Uncontrolled

TABLE 8—DATA IN CASL 8—(Continued)

Date	Weight, Lbs	Fluid Exchange		Chlorid Exchange		Phenol sul phone phthal ein	Urea Index				Chlorid Index				
		In	Out	In	Out		Blood Urea	C	D	Index	C	D	Plasma NaCl	Calcul Plasma NaCl	Thresh old
Feb 16 17	109 5	1,500	2,020	18	59										
17-18	107 5	1,500	1,980	18											
18-19		1,500	1,580	21	35										
19 20	107 5	1,500	1,220	23	10										
20 21	106 7	1,500	1,670	18	13										
21 22	108 5	1,500	1,600	18	09										
22 23	108 8	1,500	1,550	18	09										
23 24	109 0	1,500	1,028	18	11	17	0 59	5 7	8 7	9	14	- 1	5 88	5 72	5 78
24 25	107 0	1,500	1,390	18	14										
25 26	109 5	1,500	1,560	18	12										
26-27	108 3	1,500	1,460	18	06										
27 28	109 0	1,500	1,600	18	06										
28-Mar 1	110 5	1,500	2,000	18	06										
1 2	109 5	1,500	1,760	18	06										
2- 3	109 1	1,500	1,645	17	10										
3 4	108 5	1,500	1,490	17	08										
4- 5		1,500	1,520	18	08										
5 6	111 0	1,500	2,132	14	08	21	0 61	7 1	17 1	19	0 6	1 3	6 33		
6 7	110 5	1 500	1,790	17	09										
7 8	114 5	1,760	1,677	11 7	21						0 7 0 6	1 0 0 7	6 48† 6 50†		
8 9	114 5	1,500	2,060	18	27										
9 10	115 0	1,500	2,080	18	34										
10 11	112 5	1,500	1,910	18	32										
11 12	113 5	1,500	1,940	18	24										
12 13	113 8	1,500	1,780	18	10										
13 14	114 0	1,500	2,060	18	18										
14 15	113 5	1,500	1,490	18	16										
15 16	113 5	1,500	1,595	17	16										
16 17	114 5	1,500	1,840	17	12										
17 18	114 5	1,500	2,080	17	15										
18 19	113 0	1,500	1,780	18	15										
19 20		400	830	00	14										
20 21		1,625	1,820	24	22										
21 22		2,115	1,950	21	42										
22 23	111 5	2,280	2,200	29	31										
23 24	113 0	2,155	1,680	22	23										
24 25 1917	111 5	2,200	2,029	17	15	21	0 37	8 0	8 5	27	1 5	1 6	6 35	5 72	6 27
May 1						38	0 20	3 4	4 4	31	5 9	7 9	6 50	5 90	6 22

† At 10 a m

† At 11 a m, 10 gm NaCl at 10 30 a m

had a large diuresis were uniformly emaciated. The final urine examination showed albuminuria in every case but Case 2, although red blood cells persisted in only one case (4). Case 2 was accepted for the National Army in August, 1917, and the man sailed for France in January, 1918, apparently well. Cases 3 and 4, after about a year, are in perfect health and have resumed their previous work without difficulty. In Case 5 the man reports, after seven months, that he is too well to return for observation. In Case 1 the woman reports that she is sick in bed in another city. Case 8 says that he feels better than ever before in his life, although he still has hypertension and albuminuria. Case 7 had a long period of persistent edema, weakness and dyspnea, but when last seen, over a year after her admission, had no edema and was symptomatically very much improved. In brief, the final results show clinical recovery in three out of six acute cases, reported freedom from symptoms in one, and unknown illness after practical recovery in one. Neither chronic case made a clear-cut recovery, although they are both symptomatically well at present.

DISCUSSION OF FUNCTIONAL FINDINGS

The phenolsulphonephthalein test, the renal test day, the blood urea and urea index were used in the functional studies. A renal test day was done on five cases (Table 1), in each case during the last of the hospital stay and during a period of water balance as evidenced by a constant weight. The balances of salt and nitrogen, so frequently included in the performance of this test, were omitted because of the obvious unreliability of a twenty-four-hour experiment. Moreover, in view of its great dependence on a factor so variable as the amount of water excreted, systematic determinations of the specific gravity over a brief period must be very carefully interpreted. There was nocturnal polyuria in all the cases, most marked in Case 2, which in every way was the mildest. The night specific gravity was below 1.019 in all except Case 7, in which it was 1.022. The variation of specific gravity during the test day was consistently normal except in Cases 1 and 4. But since this variation is worth little more than its highest figure, indicative of the concentrating ability, we can say that every case except Case 4 showed in some specimen during its course a normal power of concentration, 1.020 or above, in fact, one of the chronic cases concentrated more highly than is seen in the average normal specimen. Of the two cases (1 and 4) showing 'maximal impairment' of the test as a whole according to Mosenthal, Case 1 did not have a subnormal renal function at any time during the period of observation, and Case 4 made a complete recovery, reaching a concentration of 1.028 some months later. It seems clear that in acute nephritis, the renal test day is of no great value, it may, indeed, be quite misleading.

The phenolsulphonephthalein excretion of the series covered a range of figures from 0 to 79 per cent, varying considerably in the individual cases and often far from consistent with the clinical and laboratory findings. If, however, only gross changes are considered, they assume a certain significance. The admission phenolsulphonephthalein was 20 per cent or less in the three most severe cases (5, 6 and 8), but in the other five, varying from 26 per cent to 65 per cent, there is little relation between the picture implied by the first phenolsulphonephthalein excretion and that found to be true by longer study. For example, Cases 1 and 2, in every way the least severe, show excretions of 28 and 44 per cent, respectively, while Cases 3 and 7 with far more persistent disease, excreted 65 and 58 per cent. But in all the cases subsequent observations fit in more satisfactorily with the rest of the picture, so that it is possible to say that the average phenolsulphonephthalein excretion gives a fair idea of the severity of the dis-

TABLE 9—DATA OF TESTS IN AUTHOR'S CASES

Case	Night Total	Night Sp Gr	Variation Sp Gr	Total Output	Weight Balance	Time in Course	Function at Time
1	765	1 013	1 008 1 010	2,220	0	Late	Normal
2	1,315	1 015	1 011-1 028	1,913	sl neg	Late	Normal
3	505	1 010	1 010 1 030	1,357	0	Late	Normal
4	612	1 010	1 008 1 012	1,254	0	Late	Phth normal Ambard 30
5			1 023 1 012*				
6			1 022 1 019*				
7	604	1 022	1 016 1 026	1,352	0	Late	Normal
8			1 014 1 026*				

* Variation during observation in hospital, no test day given

ease. These cases suggest that in acute nephritis variations above a level of 20 to 25 per cent are rarely of real functional significance, although one may add that a figure below 20 per cent is of rather more serious import, not of the immediate outcome but of the degree of involvement as demonstrated by other methods of study. Yet it is necessary to note the complete recovery of the patient, Case 4, who excreted on one occasion only 15 per cent of phenolsulphonephthalein.

Urea retention was found on admission in only three cases (5, 6 and 8), most marked in the fatal case, but above 1.2 gm per liter in each. Three of the other cases (1, 2 and 7) showed no elevation during their entire period of observation, but the remaining two patients (Cases 3 and 4) presented an unusual picture. On a low nitrogen and salt diet they retained urea steadily, reaching in the first instance a crest of 0.71 gm in two and a half weeks, and in the second a crest of 0.96 gm in five weeks. These figures decreased gradually and were normal on the patients' discharge in spite of increased nitrogen in the

diet To summarize the acute cases, the highest figure for blood urea was in the only fatal case, the other high figure was undoubtedly the next most severe and the two cases without any evidence of poor urea function were the most favorable, the blood urea estimations, therefore, have provided the most consistently valuable means of determining the degree of the process in any given case. Even here we cannot avoid noting that the chronic case, in which recovery was most delayed, showed at no time a retention of urea.

A study of the laws of urea excretion as formulated by Ambard and confirmed by McLean pictures to the reader physiologic laws so definite that they can be mathematically expressed, variables so few that they can be included in a small formula, a formula that will give exact expression of the ability of the kidney to excrete urea. On determining a number of indexes and observing the wide discrepancies found in the same person, normal or pathologic, the inclination is strong to discard the formula entirely. Further determinations, however, demonstrate that the basal laws may be applied in a very general way, and that the index, if interpreted liberally, may often contribute something of value to the diagnosis, although isolated determinations may lead far afield. In other words, as the expression of a physiologic law, the urea index is quite untenable, as are its fundamental formulae, but as a rough clinical test of one aspect of renal function, it has a place. This slight value is due to the fact that a pathologic kidney so frequently retains urea and is unable either to concentrate normally or to excrete the usual amount of urea, all factors tending to decrease renal function as expressed by the index. If we overlook variations above the normal and consider the usual rather than the average figures during a period of observation, we have in the urea index an expression of the general renal function that fits fairly well with the impression gleaned from other data. The two mildest cases (1 and 2) of our series were always normal or above, Cases 3 and 4, somewhat more severe, were more frequently below normal, while Case 6, with fatal outcome, presented the greatest impairment. Of the chronic cases, one finds in Case 7, nine out of seventeen indexes below normal, within variations from 34 to 200, and in Case 8, consistently low results throughout. In only one case (5) was there constant agreement between the Ambard and the phenolsulphonephthalein, but in the majority there were striking discrepancies, for example, in comparing the figures of Case 1 on admission and discharge, we see that the Ambard drops from 235 to 75, while the phenolsulphonephthalein rises from 38 to 64 per cent, and in Cases 2 and 3, with practically constant phenolsulphonephthalein excretions, the urea index goes from 70 to 118, in one, and from 9 to 133 in the other. But the fact remains that the average gross function expressed by the two tests agrees within the limits of clinical necessity, for forty-two subnormal Ambards were

accompanied by thirty-five subnormal phenolsulphonephthaleins, this in sixty-two observations (Assuming phenolsulphonephthalein 50 per cent and Ambard 70 as normal limits) But I would hasten to say that even moderately rigid interpretation of the Ambard as a real index of the degree of impairment of urea function may lead to the greatest error. This criticism of the Ambard is based on such observations as the following. In Case 2 at constant levels of blood urea, an increased water excretion caused a 28 per cent decrease in the index, although the rate of excretion (D) was the same, February 28, volume of urine, 94 c c, blood urea, 0.38 gm, rate D, 22.5 gm, index, 98, March 14, volume of urine, 204 c c, blood urea, 0.37 gm, rate D, 22.4, index 70, while in Case 3 the apparent function was higher when the kidney excreted at the rate of 7 gm than when it excreted 13 gm. June 21, the blood urea was 0.29 gm, urine concentration 9.4 gm, rate D 7.0 gm, index 32, and on July 12 the blood urea was 0.28 gm, urine concentration 1.7 gm, rate D 13.4 gm, index 27.

Four observations under constant conditions on Case 4 with rates of excretion varying less than 0.5 gm showed indexes from 22 to 50 due mainly to small fluctuations in the blood urea. Case 8 had a rate of 2 gm during a period when the blood urea was decreasing and a rate of 10 gm during retention, although the blood figures at the two observations were the same.

While the wide variations of the urea index are not always accompanied by comparable changes in renal function as judged by other means, yet these results have a certain scientific interest. The most striking observation in the series is the fact that there was in every case a drop in the index during clinical improvement. In Case 1 a decrease from 235 to 75 unaccompanied by any other evidence of functional change has only an exceptionally low blood urea (0.1 gm per liter) in the first observation to explain the higher figure. Two months after the lower figure (75) was found, another determination was made and with an unchanged blood urea a 40 per cent increase in the water output raised the index to 111. Case 2 immediately after diuresis fell from 98 to 70, although the blood urea and total excretion (D) were constant. One month later, the extraordinary figure of 531 was obtained, notwithstanding the fact that the rate of excretion was practically the same as that of the other six observations, explicitly it was 20 gm as compared with an average of 19 gm on previous determinations ranging from 16 to 22 gm. There were too few observations on Case 5 to permit satisfactory discussion of his results, but here again there is a drop from 18 to 9 after diuresis, although the patient continued to improve. While these three cases are similar in a lowered urea index after marked clinical improvement, there is in no case an accompanying change in the other tests of renal function, in particular, no urea retention, and in Cases 1 and 2 the

changes are seemingly due to the vagaries of the formula. There is, however, quite a different picture in Cases 3 and 4, in which the falling Ambard is paralleled by a retention of urea and a moderate decrease in the phenolsulphonephthalein excretion. Case 3 during a remarkable diuresis, losing 38 pounds in nine days, went from 0.27 to 0.45 gm per liter, and after coming into balance eight days later the figure was 0.71 gm. During this time the index dropped from 65 to 9, although the rate of output (D) was the same for both observations. Meanwhile, the nitrogen intake was constant and there was no change in the patient's general condition. Case 4 lost very little weight, but the blood urea increased steadily from 0.27 to 0.96 gm per liter in a period of five weeks, while her index dropped from 28 to 5. Her nitrogen intake was decreased from 10 gm to 5 gm one week after the first sign of retention. In both cases the urea fell from its highest figures to normal in about ten days, with a coincident rise in the Ambard and phenolsulphonephthalein but with no other observed changes. It is important to point out the absolute clinical unsimilarity of these two cases. There was no significant abnormality of salt function accompanying this phenomenon.

This puzzling urea retention while the patient is recovering may be due to a general impairment of renal function, or, overlooking the rather inconsistent phenolsulphonephthalein variations, to some change in the urea mechanism. Mason's⁵ suggestion that the first normal figures are due to a stimulated function requires the rather difficult assumption that the process, the nature of which is unknown, markedly impairs the renal function for water and salt, while at the same time it stimulates the urea function. Moreover, since every case but one (Case 1) in this series returned to a function at least as high as the original one, under "stimulation," it seems more probable that the original figure was merely a fairly normal one, while the "slump" was due to some factor occurring in the course of the disease. It is obvious that the retention is too much delayed to be a phenomenon of blood concentration. An increased blood urea may be due to an unusual presentation of urea to the body, here we have two factors to be considered, the low caloric diets forcing use of body protein and the considerable wasting during diuresis. But both these factors were present in Case 2, while in Case 4 an early decrease of 5 gm in the nitrogen intake did not influence the course. The other obvious manner of increasing the blood urea is by a lowered power of excretion. There may have been renal fatigue due to the large excretion of water or salt, but the striking diuresis in Case 2 was not thus effective. Since we know nothing of the nature of this disease, or diseases, we can, of course, suggest that this curious functional change may be part of its

⁵ Mason THE ARCHIVES INT MED, 1918, 21, 261

natural course The most convincing argument that a decreased urea function was not instrumental is the picture in Case 4 Here we have an increase of blood urea in a rate of excretion (D) of 6 to 15 gm, and a decrease on a constant excretion of 4 gm (four observations), over a period of six weeks, in other words, during retention the kidney was excreting urea much better than when there was the opposite reaction What difference can it make that the kidney was working under the stimulus of a greater blood urea when it was excreting at the higher rate? If the kidney could take care of a certain intake of nitrogen with a rate of 4 gm, it should certainly do so with a rate of 15 gm The writer realizes that the essential weakness of this argument is that his rate (D) is calculated from an isolated two hour observation, as is Ambard's index, but the consistent difference between the two sets of figures may lessen the weight of this criticism Where, then, may we seek an explanation of this retention if we cannot find an increased production of urea or a definite decrease in the ability of the kidney to excrete it If we decline to consider the kidney a fixed and unchanging valve in the bottom of a cylinder of blood, and remember that it is of the same fundamental substances and subject to the same laws that apply to blood, then we cannot be so exacting in our demand for a mathematical relationship between the blood urea and urine urea Since this organ of excretion is itself so largely composed of blood, it seems obvious that its function cannot be expressed by a constant but will depend on the physico-chemical changes that may occur in the blood There may, therefore, be shifts in the constituents of the blood that will not be mirrored by the urine In Case 6 a rising blood urea is accompanied by a fall in the plasma chlorid to the extremely low level of 4.45 gm per liter, although there had been complete retention of chlorids for a period of some weeks This change may be due to a shift in other blood constituents, and was probably necessary to preserve the osmotic relations We have discussed this "recovery retention" at greater length than our material deserves, because it seems to point to variables not recognized by our present formulae of urea excretion

It is interesting to consider the widely varying urea indexes found in these patients in view of McLean's⁶ suggestion that fixation of the index is a sign of moderate renal impairment Case 7, for instance, with chronic renal disease, varied from 34 to 200, others varied even more strikingly

DISCUSSION OF SALT AND WATER EXCHANGE

Edema was present in every case In two cases, 1 and 4, it had so greatly diminished before admission that there was no striking diuresis under observation These patients lost a little weight and swept out

6 McLean Jour Exper Med, 1917, 26, 181

small quantities of salt, but they came very quickly into equilibrium and remained so. Case 6 was never able to excrete salt or water and his edema steadily increased until death. There was in Case 5 a continued loss of weight amounting to $35\frac{1}{2}$ pounds for the month of observation, and the patient's salt and water balances were consistently negative. Two cases, however, showed a remarkable diuresis, Case 2 lost 30 pounds, and Case 3, 41 pounds in eleven days, the daily losses reaching as high as 10 pounds. The decreasing edema was accompanied by a great sweeping out of salt and water, but after reaching a constant weight neither patient showed any abnormality of salt or water function in the daily balances.

The sequence of events in diuresis was possible of study in Case 2 and in certain periods of Case 7, one of the chronic cases who had alternate periods of increasing and decreasing edema. It seems clear that the salt function is the first to be regained, followed at varying intervals by the pouring out of water with a coincident decrease in weight. Case 2 was excreting comparatively little water the first day of admission, but had already begun to put out large quantities of salt, the next day the water elimination more than doubled with a quite disproportionate increase in salt excretion. Events moved so rapidly here that a close analysis is impossible, but in Case 7, at one period the salt excretion began steadily to increase ten days before the increase in water excretion or the drop in weight was evident. This relationship of the salt excretion to diuresis is confirmatory of other known facts that point to a very close relationship between chlorid function and edema. Another feature of the mechanism demonstrated by Case 2 is the fact that the water loss by urine and stool during diuresis covers a surprisingly low percentage of the weight loss for the period. Over two periods, one entirely accurate and the other practically so, this case had daily water loss of 1,110 cc, and 1,285 cc, respectively, to be accounted for by vaporization. This is a definite increase above normal and demonstrates that the skin and lungs may assume a large share in the excess excretion of water. It is interesting to note that the amount of chlorids that should theoretically be excreted, were the weight lost a solution with the concentration of the blood, agrees fairly well with actual salt loss. In Case 2, over a seven day period the theoretical figures for a 12.7 kg loss of weight would be 76 gm, and actual loss was 63 gm. Case 3 in seven days lost 76 gm compared with a calculated 78 gm, and in Case 5 for twenty-five days it was 94 gm theoretical, 74 gm actual. Of course, these balances are not entirely accurate, for the chlorids of stools and sweat were not estimated. Nevertheless, they are sufficiently close to suggest that there is no storing of chlorids in concentrations above that of the blood. Four of the cases were given varying amounts of added salt during convalescence and in no case was there gain in weight or failure to

handle the extra intake, which was 3.3 gm in Case 1, 4.6 gm in Case 2, 8.8 gm in Case 3, and 2 gm in Case 4. It may be added that the course in Case 3 seemed to point out that over 8 gm was too much to be given safely in these cases. Both of the chronic cases gained weight when salt was administered, and it is worth noting that in salt function only did their findings differ characteristically from the acute cases.

The concentration of chlorids in the plasma was generally at its highest point on admission and decreased during diuresis in every instance, the greatest drop was 0.65 gm per liter in Case 5, and the most rapid drop was in Case 2, in which it fell 0.35 gm in three days. Although the association of a high concentration with marked edema is apparently another result confirming the causative rôle of chlorids in this abnormal accumulation of fluid, it must be noted that three of the cases returning without edema after a period of ordinary diet had high figures, so it is possible that the low chlorid diet under treatment accounts for this drop after admission. The plasma chlorid was always lower during a salt poor diet, increasing with the addition of more salt, but the variations thus caused were relatively small, the greatest increase was only 0.23 gm per liter in Case 3, after several days of 8.8 gm of salt a day. One of the most interesting observations was the marked fall in concentration in Case 6 (from 6.19 to 4.45 gm per liter) over a period of practical suppression of urinary chlorid excretion. Subcutaneous edema fluid, uncontaminated by blood, obtained at operation, showed the same low figure, as did also the chest fluid, we may, therefore, assume a fairly general fall in body fluids. There was a coincident increase in edema, but it was not sufficient to charge the change in concentration to dilution of the blood, as the following calculation will show. At a concentration of 5 gm to the liter, an increase in weight of 7.7 kg would require 38.5 gm of salt to bring its concentration to that of the blood, whereas the amount of salt given up by 56 kilograms of body fluids (70 per cent of the body weight) in a drop of 1.67 gm per liter, would be 66 gm, and there was, moreover, a positive balance, intake and urine output, of practically 50 gm. It is clear, therefore, that we may have a gradually increasing total salt content in the body with a diminishing concentration in the plasma not due to dilution by fluid retention. We are forced to consider it a shift due to changes in the physico-chemical environment. At least two possibilities are suggested by this case, one is the forcing of the chlorids into the corpuscles by change in the carbonate concentration, the Zunst⁷ reaction, or, an increase in other blood constituents, such as the high blood urea, may demand a readjustment to preserve the osmotic balance. In any case, we have

7 Zunst. Beitr. z. Physiol. d. Blutes, Bonn, 1868.

the illuminating fact that there may be a very great change in the plasma chlorid concentration independent of intake or urinary excretion, and paradoxical to the apparent chlorid balance

In no case was the rate of excretion clearly dependent on the concentration of chlorids in the plasma. In general, the latter tended to remain quite constant when equilibrium was established after diuresis, while the urinary output was proportional to the daily intake of salt. With identical plasma chlorids the rate of excretion showed the widest variation under different dietary régimes. For example, Case 2, with a constant plasma concentration, excreted at a rate of 0.6 gm. on a salt poor diet, and at 13.6 gm. when 4 gm. of salt were added daily to the intake, Case 3 with 6.13 gm. per liter in the blood excreted 2.2 gm. on a very low intake, while seven days later with an increased intake his excretion was 9.2 gm. and the plasma 6.15 gm. per liter, Cases 1 and 4 show the same relation to a lesser degree. It would be difficult to ascribe these variations to changes in the course of the disease. If the rate of excretion is so independent of the plasma concentration it is evident that the threshold according to McLean's formula could be greatly changed by the ingestion of salt. As a matter of fact, we find it changing in Case 2 from 5.84 on a salt poor diet to 5.58 on an intake of 4 gm. a day, and similarly in Case 3 from 6.25 to 5.9. The reaction to a single administration of 7 gm. of salt is interesting. It is most clear cut in Case 2, in which there is a rise in plasma concentration of about 0.2 gm. with no change in excretion, although forty-eight hours later, with the same plasma chlorid, the rate of excretion has increased seven times. Obviously, some other factor than the concentration of chlorids in the plasma was responsible for the increased excretion.

The fundamental theory of the chlorid index requires only the foregoing data to demonstrate its physiologic impossibility. We have published elsewhere⁸ even more conclusive evidence of the effect of dietary modification on the chlorid threshold in normal individuals. But the clinical value is quite aside from the accuracy of the formula, and if we find a fairly consistent relationship between the threshold and the severity of the disease, we may consider the test of value. As a matter of fact, while the threshold is elevated in almost every case and is highest in the severest case, practically every high threshold depends on one of two factors, a low excretion due to a very low intake, or a plasma concentration considerably higher than normal. Of course, this increased concentration may be caused by a raised threshold, but Case 6 with a threshold of 6.1 at admission decreased his concentration to an extraordinary extent, although the urinary

⁸ Atchley, *Proc. Soc. Exper. Biol. and Med.*, 1918, **15**, 85

excretion showed no evidences of increased renal permeability to salt. Since any threshold determined during a salt-poor régime is entirely misleading, the frequency of this régime in nephritis makes the clinical application of the chlorid index rather limited. This much is clear, there is no definite constant threshold for any individual, nor is the height of the threshold an index of the degree of impairment of chlorid function. More valuable than what the formula expresses are the facts that may be gathered from a determination of the plasma chlorid concentration, together with a knowledge of the daily intake and output of salt. There are fairly conclusive grounds for saying that an abnormally high plasma chlorid on a moderate salt intake may be the only evidence of a latent disturbance of chlorid metabolism.

THERAPY

Since the fundamental principles that underlie this disease are still a mystery, all attempts at therapy must take the most general lines. There is fortunately one brilliant exception in the relation of sodium chlorid to edema, a relationship long known if little understood. The first step in the treatment of acute nephritis is, therefore, restriction of the sodium chlorid intake. Beyond this move, the general principles suggested by this study may be briefly recounted, remembering always that each case is a distinctive picture and will require distinctive treatment. The caloric requirement of the patient should be maintained from the very beginning, in as palatable a form as is possible, and after diuresis has occurred he should be moderately overfed. Empirically, it is wise to give a low protein intake in all cases of acute nephritis, the degree of restriction depending largely on the amount of urea in the blood. To be more explicit, when there is no retention of urea, 8 or 10 gm of nitrogen is a safe intake, but if there is an abnormal figure, 6 gm should be the upper limit. The latter amount should not be exceeded if gross hematuria is present. Theoretically, the urea index should give us the most valuable information about the ability of the kidney to handle nitrogenous foods, but the facts presented demonstrate its unreliability for that purpose. (Case 3 was increasing his blood urea with an index of 25, while Case 5 was decreasing his at an index of 15). While a limited (1,200 cc) fluid intake is the method of choice, fluids may be forced (2,500 cc) with benefit in certain stubborn cases, particularly if there be nitrogen retention. The patient should be confined to bed until diuresis is complete, as evidenced by a week of fairly constant weight, although gross hematuria is always a contraindication to being out of bed. One cannot escape the conclusion that our therapy here is merely an attempt to prevent traumata that would interfere with nature's readjustment of forces unknown at present.

GENERAL SUMMARY

Any attempt to classify this series on an anatomical basis would of necessity be entirely speculative and will, therefore, be omitted. Moreover, until there is some definite knowledge of the physiologic anatomy of the kidney, the cataloguing of clinical pictures by anatomic names seems to be unjustified and confusing. If there be hematuria we can say that there probably is some degree of acute inflammation and treat the case accordingly. But beyond that a diagnosis such as glomerulo-nephritis is incomplete, perhaps unfounded, and does not contribute in any way to the treatment of the case. The duration of the pathologic process previous to the appearance of symptoms is another point quite impossible to determine, and if it were possible to guess fairly accurately, little of value would be contributed thereby. Case 7, for instance, is called chronic merely because albuminuria was accidentally discovered some years before the present attack, which otherwise was of an acute onset fairly similar to those of the true acute cases.

These patients are grouped together because they became acutely ill with the constant presence of edema, albuminuria and hypertension, findings of so-called renal origin. A closer analysis of the individual cases proves each to be a separate and distinct picture. It is quite impossible to subdivide them further without omitting one or more essential points of difference. One is also unable to predict the course or outcome from the original picture on admission. Prognosis is, therefore, very unsatisfactory. Every case is an individual problem and only by means of a careful study over a moderately long period of time can its status be determined. This study should confine itself to the scope of our knowledge of the pathologic physiology of renal function. First of all, the salt function determined by the concentration of chlorids in the plasma, together with the daily chlorid balance, second, the water balance discovered by frequent weighings and observation of the fluid exchange, and last, the urea function as demonstrated by the height of the blood urea on a known nitrogen intake. Other factors such as hematuria, anemia, or hypertension are, of course, important, but secondarily so. In treating diabetes we are satisfied, clinically, with its simple terminology and proceed to investigate the peculiarities of the disease in a particular individual. In like manner, it would seem logical to call the type of case described in this paper an acute renal syndrome and investigate the variations in function peculiar to each case without demanding that every variation be added to the terminology of the diagnosis.

In conclusion, one must express the feeling that the investigation of this disease has been hindered by an interest too closely restricted to the kidneys. A broader study of the chemical balances of the body as a whole may demonstrate that the kidney is of secondary importance.

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A CLINICAL STUDY OF PNEUMONIA BASED ON EIGHT HUNDRED AND SEVENTY-ONE CASES

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INTRODUCTION

Only completed cases of pneumonia treated at the U S Army Base Hospital, Fort Riley, Kan, during the seven months' period, Oct 18, 1917, to May 18, 1918, are included in this report (Fig 1) This series is made up of 668 instances of lobar pneumonia, 181 instances of measles pneumonia,¹ and 22 instances of bronchopneumonia During the period, Oct 1, 1917, to May 18, 1918, there were 22,854 admissions, making a total incidence for pneumonia of 4.5 per cent Of the 668 completed instances of lobar pneumonia, 154 patients died, a mortality of 23 per cent Of these 154 deaths, 87 were complicated by empyema The mortality of lobar pneumonia without empyema was therefore 12.7 per cent

During the period, Oct 18, 1917, to May 18, 1918, 2,956 cases of measles were treated in this hospital The total number of measles pneumonia has been 181, making, for the period, an incidence of pneumonia in measles of 6.1 per cent Of the 181 cases of measles pneumonia, 83 patients have died, a mortality of 45.8 per cent Included among these 83 deaths, were 43 deaths from empyema The mortality of measles pneumonia without empyema was therefore 32.5 per cent There were, in addition, twenty-two instances of bronchopneumonia not included in the measles group Among these there were no empyemas, but there were two deaths, a mortality of 9 per cent

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1 The term "measles pneumonia" refers to pneumonia following measles It was impossible, in many instances, to distinguish, clinically, lobar from bronchopneumonia, especially if empyema was an early complication

Table 1 brings out the mortality incident to these different groups with reference to empyema

TABLE 1—MORTALITY WITH REFERENCE TO EMPYEMA IN PNEUMONIA

Lobar Pneumonia	Number	Number of Deaths	Mortality, Per Cent
With empyema	142	87	61.2
Without empyema	526	67	12.7
Total	668	154	23.0
Measles Pneumonia			
With empyema	58	43	74.1
Without empyema	123	40	32.5
Total	181	83	45.8

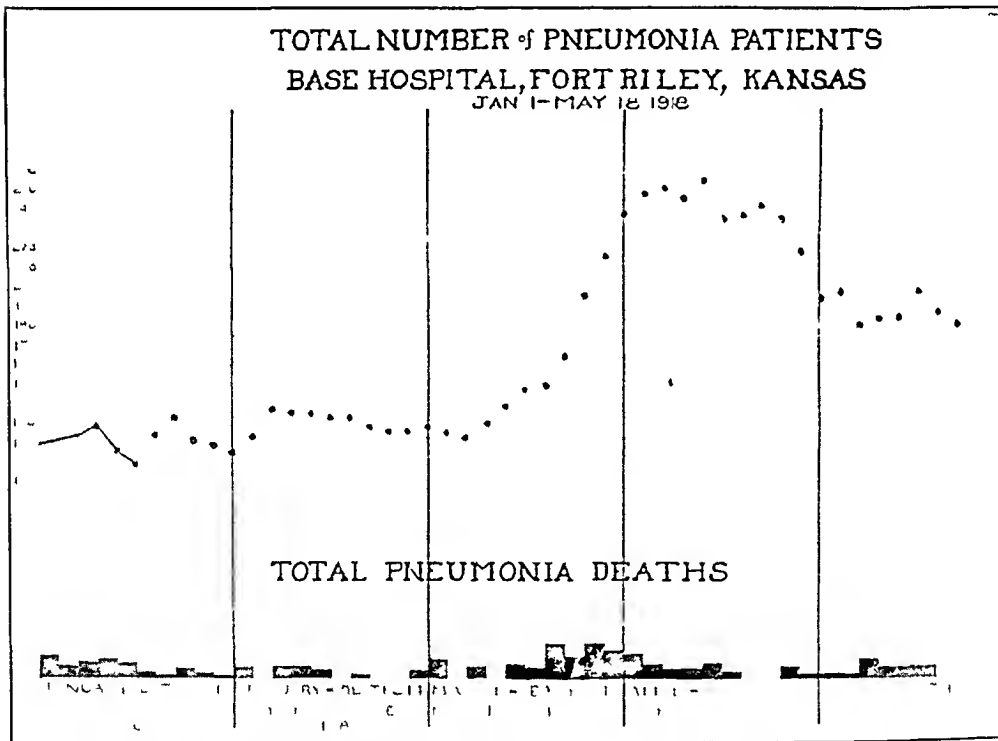


Fig 1—Graphic representation of total number of pneumonia patients at the Base Hospital, Fort Riley, Jan 1 to May 18, 1918

DISCUSSION

It will be seen that the mortality in lobar pneumonia was about half the mortality of the pneumonia following measles (23.45.8). It has been instructive to observe the varying mortality from month to month depending on features difficult to interpret except on the basis of differences in the virulence of the infection. Table 2 emphasizes this fact and shows how, irrespective of every facility for proper care, the mortality with the same general plan of treatment varied from month to month.

TABLE 2—VARIABILITY OF MORTALITY BY MONTHS
LOBAR PNEUMONIA

	Number of Completed Cases *	Number of Deaths	Mortality, Per Cent
January	77	21	27.2
February	63	9	14.2
March	118	45	38.1
April	165	25	15.1
May	115	14	12.1

MEASLES PNEUMONIA

January	40	11	27.5
February	20	5	25.0
March	4	1	25.0
April	30	8	26.6
May	9	3	33.3

* The term "Completed Cases" is used to designate patients discharged from hospital either to duty or death

Empyema was the most frequent and the most serious complication met with in lobar pneumonia as well as in measles pneumonia. This is shown in Table 3.

TABLE 3—EMPYEMA INCIDENCE IN PNEUMONIA

	Total Cases	Empyemas	Incidence, Per Cent
Lobar pneumonia	668	142	21.2
Measles pneumonia	181	58	32.0
Bronchopneumonia	22	0	0
Total	871	200	22.9

PER CENT OF EMPYEMA DEATHS TO TOTAL DEATHS

	Total Deaths	Empyema Deaths	Per Cent
Lobar pneumonia	154	87	56.5
Measles pneumonia	83	43	51.6
Bronchopneumonia (not measles)	2	0	0
Total	239	130	54.3

That the fatality of this complication (empyema) varies likewise from month to month under the same general plan of treatment is shown in Table 4.

TABLE 4—FATALITY OF EMPYEMA BY MONTHS

LOBAR PNEUMONIA

	Completed Empyemas *	Deaths	Mortality, Per Cent
February	8	3	37.5
March	34	29	85.3
April	22	14	63.6
May	33	7	21.2

MEASLES PNEUMONIA

February	5	4	80.0
March	2	0	0
April	13	4	30.7
May	4	2	50.0

* Many of these patients were admitted in earlier months but did not figure as completed cases until the month specified.

It will be noticed from Table 4 that the highest mortality in which empyema was the prominent associated pathologic condition occurred during the months of March and April. These were largely instances of overwhelming infection of rapid onset and death within a few days. The type of infection and the associated pathologic condition will be discussed under pathology.

CLINICAL DIAGNOSIS

It will not be necessary to lay stress on the varying clinical features of lobar pneumonia. The rapid onset of chill, fever and cough with tubular breathing and signs of consolidation, however small, sufficed, in the vast majority of cases, to establish the diagnosis. Abortive cases were occasionally seen in which, after twenty-four hours, all signs of tubular breathing and consolidation had disappeared. These were not included in the statistics.

The roentgenogram may be of great help in making a diagnosis of questionable consolidation. The patient, shortly after admission, should have a chest plate taken. Roentgenograms have been taken of the chests of patients in about 250 completed pneumonia cases. Consolidation may not infrequently be detected by this means before definite physical signs warrant a positive diagnosis. Such a plate serves the purpose of comparison with plates subsequently taken in the diagnosis of complications.

In the diagnosis of bronchopneumonia some dependence should be placed on the history of previous bronchitis or measles. The signs of bilateral involvement without definite areas of consolidation and the presence of moist crackling râles, especially during inspiration, were usually sufficient to establish the diagnosis. Unilateral bronchopneumonia was not infrequently observed. In bronchopneumonia the dyspnea was usually more marked, the accessory muscles were used in inspiration, cyanosis in many instances was a prominent feature, the sputum of a particularly ropy character, and the patient presented the picture so well described in the older term of "suffocative catarrh."

In the diagnosis of complications (Fig. 2) the aspirating needle was used early for the detection of empyema. Increased frequency in respirations or pulse rate, the presence of cyanosis, so-called "delayed resolution," a decreased fever but with increased pulse rate, should be sufficient reason for suspicion of this common complication.

Pus was frequently found without any increase in the temperature. The rule was that if either the temperature, pulse or respirations remained elevated, search was to be made for physical signs of fluid in the chest. Seldom were all the physical signs of fluid present, but if any one sign was present, paracentesis was justified. Skoda's resonance was present in large effusions. Weakened breath sounds,

diminished tactile fremitus with decrease in vocal or whispered voice resonance were the most valuable signs. Bronchophony was noticed in some instances or the voice sounds possessed the peculiar nasal twang described by Laennec as egophony. The roentgen ray was of little help in small accumulations of fluid, but was of great help in outlining larger accumulations associated with fibrinoplastic pleural thickening.

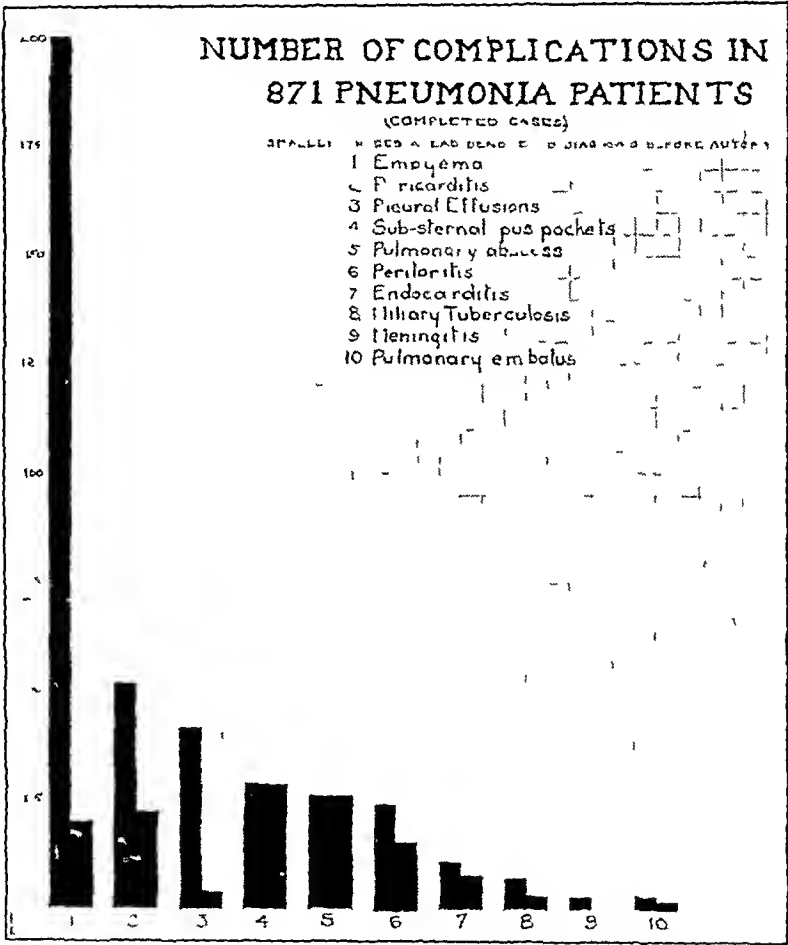


Fig 2—Complications in 871 pneumonia patients

In performing pleural puncture it has been found beneficial to remember that the diaphragm may be higher on the affected side than is commonly believed, due to abdominal distention. The point usually selected was over the area of greatest dullness, after outlining the upper limit of the liver in front and side if puncture was to be done on the right side. Behind, below the angle of the scapula, or laterally in the post or midaxillary lines were the usual locations for puncture. In accumulations in front the nearer the puncture to the sternum the greater the danger because of the internal mammary artery and the larger vessels.

The leukocyte count was not of great value in the detection of complications, as will be seen from Table 5. It will be noticed that the average counts were higher in bronchopneumonia than in lobar pneumonia.

TABLE 5—THE LEUKOCYTE COUNT IN PNEUMONIA

	Uncomplicated Cases	Complicated Cases
Lobar pneumonia	64	28
Average count	14,960	16,100
Bronchopneumonia	10	7
Average count	20,450	19,650

Pericardial effusion was suspected when any diminution in the clearness of the heart tones became evident, particularly if this had been associated with an earlier definite friction rub synchronous with the heart beat. If signs of fluid, as evidenced by an increase in heart dulness, were apparent, paracentesis of the pericardial sac was done, in no instance with apparent damage. The point selected was usually slightly below and outside the nipple, the needle pointing upward toward the inner third of the left clavicle and backward. In one instance over 1,000 c c of fluid were removed in three aspirations. As will be observed in Table 6, serofibrinous or purulent pericarditis was found at necropsy in 51 instances, of which 22 were not diagnosed prior to death. Many of these showed friction sounds at some time during the course of the disease which could not be differentiated from a pleuropericardial friction rub, especially when associated with hyperpnea and rapid pulse. Pericarditis occurs frequently enough in pneumonia to make it an imperative rule to examine the heart with care at each visit. Serofibrinous pericarditis occurred clinically in approximately 4 per cent of lobar pneumonias, in 22 per cent of measles pneumonias. There were 31 instances. Twenty-four of the patients died. Pericarditis purulenta occurred only in association with empyema of subcostosternal pus pockets. Of this complication there were 20 instances, in all of which death occurred. At necropsy the pericardium was found distended with quantities of purulent fluid varying in amounts from 500 to 1,000 c c. In patients coming to necropsy at a later stage the visceral layer of the pericardium and myocardium was covered with thick organized exudate producing the picture of the "shaggy heart." In one instance erosion of the muscle of the left ventricle had occurred, with fibrous thickening in the region of the A-V bundle, which had produced auricular fibrillation and a marked pulse deficit before death. The pus showed long chains of streptococci.

Diphtheria was simulated in two instances by edema of the glottis incidental to a streptococcic infection. The larynx should be examined

by means of a laryngeal speculum in any questionable case of beginning stridor, since the Klebs-Löffler bacillus is not an infrequent visitor to pneumonia wards

Acute peritonitis was diagnosed in five moribund patients in whom the condition was not found at necropsy. Ascites was mistaken for peritonitis in one instance. These conditions were simulated by abdominal distention due to toxic ileus. This tympanitic distention so frequently seen in pneumonia has been believed to be similar in nature to the so-called "paralytic ileus" following abdominal operation. That it is due to toxemia in pneumonia we have little doubt. In a number of necropsies on patients in whom this had been a prominent symptom there were found localized areas of the descending colon, 4 or 5 inches long, involved in spastic contracture. These areas involved the sigmoid and splenic flexure of the colon particularly. There were usually not more than two such areas involved. The colon above these areas of contracture was enormously distended with gas while the contracted areas were empty. The condition then resembles a spastic rather than a paralytic ileus. It deserves further study because of the divergent methods of treatment required properly to relieve the condition. This will be discussed under treatment. Peritonitis occurred only in connection with empyema. The extension was through the diaphragm on the side subjacent to the empyema. The abdominal surface of the diaphragm in these instances was covered with fibrinopurulent plaques of exudate. At a later stage general diffuse peritonitis was present.

As will be noticed in Table 7, showing the failures to diagnose the various complications, endocarditis was not diagnosed in 72 per cent. In a number of instances the endocardial lesions were slight, but were sufficient to attract attention at necropsy. In many instances (exact number not recorded), the heart dulness was observed to be increased to the right during the course of the disease. At necropsy the right side of the heart was found to be distended and apparently dilated, while the left ventricle was found to be firmly contracted in systole, probably as a result of the influence of digitalis administered to physiologic effect. This will be discussed under treatment. In one instance an open foramen ovale was found undiagnosed until necropsy in a patient with a typical "shaggy heart," the entire pericardium being filled with organized fibrinoplastic exudate.

It will be noted in Table 6 that subcostosternal pus pockets were found in 29 instances in 153 necropsies, and that the diagnosis was not possible prior to death in any case, although the presence of such purulent accumulations were suspected in many instances from the combination of clinical and roentgen-ray evidence. An explanation of the presence of these pockets in this location is offered in the descrip-

tion of the accompanying drawing (Fig 3) This pocket of pus, which is usually situated on the side of the affected lung, but which may be bilateral, lies immediately beneath the sternum It occupies the space between the median flap of lung composing the upper lobe as it lies above the fibrous layer of the pericardium It is not in the mediastinum and should not therefore be called a mediastinal abscess

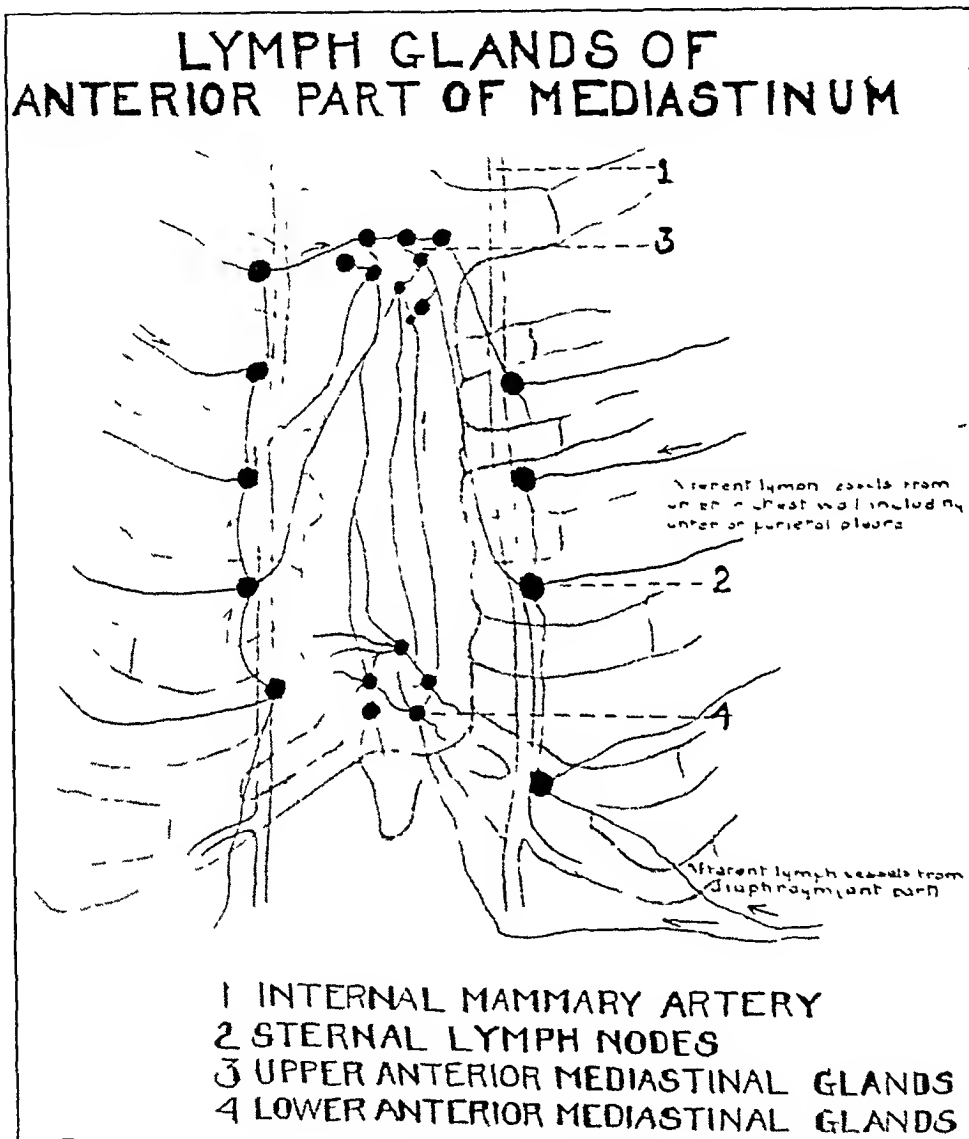


Fig 3—Diagrammatic representation of the lymph glands anterior to the mediastinum indicating possible location of pus pockets

The term subcostosternal pocket describes the location and its boundaries. The pocket may communicate with other septal pockets or other portions of the pleura of the affected side. The vessels of the hilum may be its deepest limit or the opening to the pleura may occur through the normal pulmonary septa. This pocket is almost impossible

to drain laterally, anteriorly or posteriorly by the usual thoracotomy or costatectomy. This pocket may be primarily affected and all other portions of the pleura be apparently free from pus while this one alone remains undrained and unhealed.

TABLE 6—THE TEN MOST COMMON COMPLICATIONS IN PNEUMONIA BASED ON 871 COMPLETED CASES (153 NECROPSIES), BASE HOSPITAL, FORT RILEY, KAN.

	Number	Incidence, Per Cent	Not Diagnosed Before Necropsy, Per Cent
1 Empyema	200	23.0	10.0
2 Pericarditis	51	5.9	43.0
3 Large pleural effusions	42	4.8	9.5
4 Subcostosternal pus pockets	29	3.3	100.0
5 Pulmonary abscesses	26	3.0	100.0
6 Peritonitis	24	2.7	62.5
7 Endocarditis	11	1.2	72.0
8 Miliary tuberculosis	7	0.8	43.0
9 Meningitis	3	0.3	0.0
10 Pulmonary embolism	2	0.2	50.0

Thirty-three per cent of pneumonia patients develop one or more complications.

This table does not take into account such readily diagnosed complications as otitis media or arthritis.

TABLE 7—PROBABILITY OF THE CORRECT DIAGNOSIS OF THE COMPLICATIONS OF PNEUMONIA FOUNDED ON 153 NECROPSIES

	Found in, Per Cent
1 Large pleural effusions	90.5
2 Empyema	90.0
3 Pericarditis (serofibrinous and purulent)	57.0
4 Miliary tuberculosis	57.0
5 Pulmonary embolism *	50.0
6 Peritonitis (subdiaphragmatic or diffuse)	37.5
7 Endocarditis	28.0
8 Subcostosternal pus pockets	0.0
9 Multiple pulmonary abscesses	0.0

* Two instances only.

If the infection traveled by way of lymphatic vessels from the lymph spaces in the alveoli of the lung and perivascular and peribronchial lymphatics it would reach the middle mediastinal lymph glands just below the bifurcation of the trachea, from which it would communicate to visceral nodes in the anterior and posterior mediastinal spaces and would produce a mediastinal abscess. We believe that the course of the infection is parietal rather than visceral, that it follows the lymph channels to the pleura from which afferent lymph vessels, draining the anterior chest wall including the anterior parietal pleura, lead to sternal lymph nodes of which there are usually six on each side along the course of the internal mammary arteries. The pus pockets occur in close proximity to these nodes due undoubtedly to breaking down of these glandular structures. They have constituted a unique and very serious complication.

So-called toxic arthritis occurred in ten instances of empyema. But one patient developed a suppurative arthritis in association with empyema in this series.

Blood cultures were taken from 100 patients with pneumonia, or suspected pneumonia, on admission. In one instance a hemolytic streptococcus was obtained from a patient with bronchopneumonia whose sputum also contained the same organism. In five instances a

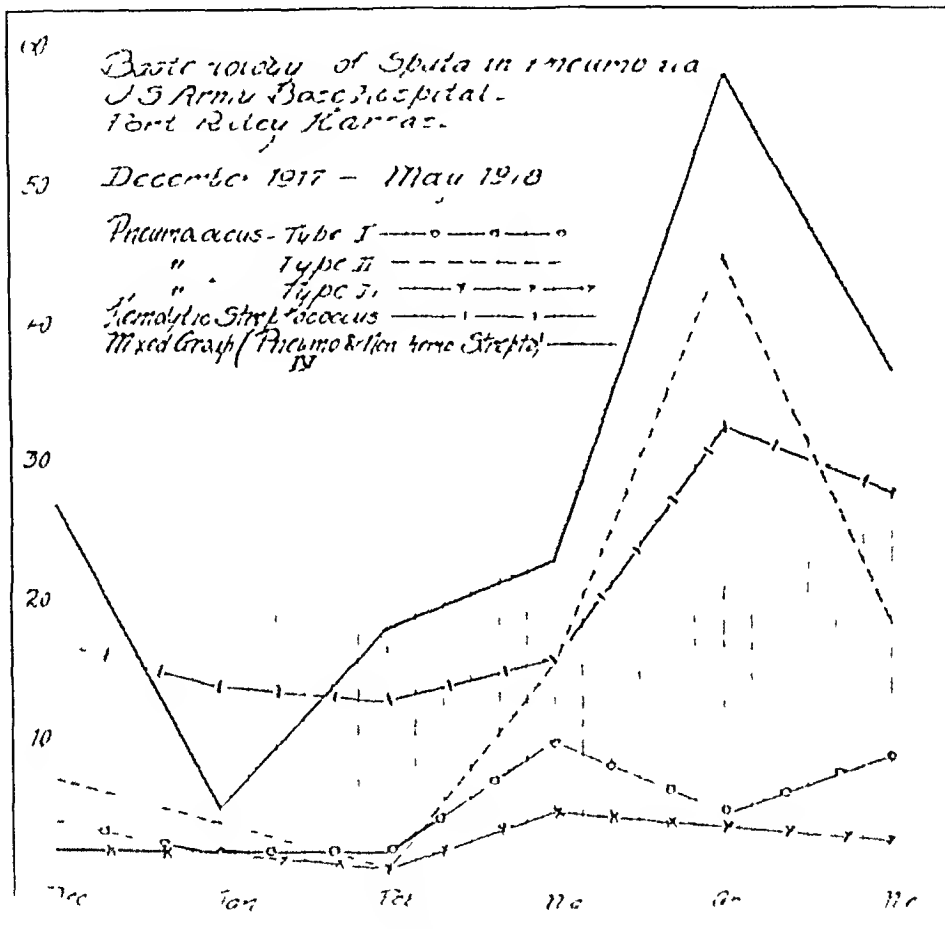


Fig 4—Curves representing the incidence of the different types of bacteria in the sputa in pneumonia

pneumococcus was obtained, in two of which the patients did not develop pneumonia. The cultures were sterile in 94 per cent. Blood cultures have not therefore been of much assistance in this study of pneumonia. We have been impressed with the infrequency of ulcerative endocarditis, of phlebitis, of splenic or kidney infarcts or of meningitis as contrasted with the frequency of empyema, pericarditis and peritonitis in this study. This indicated spread by way of the lymphatics rather than by the blood stream.

TYPES OF INFECTION IN PNEUMONIA

During the interval, December, 1917, to May, 1918, sputum determinations as to type of infection were made in the hospital laboratory² in 428 completed cases of pneumonia

TABLE 8—BACTERIOLOGY OF SPUTA IN COMPLETED PNEUMONIA CASES

	Dec	Jan	Feb	Mar	Apr	May	Total	Per Cent
Pneumococcus Type I	4	2	2	10	5	9	32	7.7
Pneumococcus Type II	7	4	1	16	43	19	90	21.0
Pneumococcus Type III	2	2	1	5	4	3	17	3.9
Hemolytic streptococcus	17	14	13	16	33	28	121	28.2
Mixed Group (Pneumo IV and Nonhemolytic streptococcus)	27	5	18	23	58	37	168	39.2
Total							428	

In 155 empyema fluids the hemolytic streptococcus was found in 106, or 68.4 per cent, the nonhemolytic streptococcus in 9, or 5.8 per cent. Table 9 shows the relation of streptococcus infection in the empyemas of lobar and measles-pneumonia

TABLE 9—BACTERIOLOGY OF 155 COMPLETED EMPYEMAS

	Lobar Pneumonia	Measles Pneumonia	Total	Per Cent
Pneumococcus	32	8	40	25.8
Streptococcus, hemolytic	75	31	106	68.4
Streptococcus, nonhemolytic	2	7	9	5.8
Total	109	46	155	

Table 10 brings out the mortality of the types of infection in 155 instances of completed empyema. It will be seen that the mortality in empyema, due to the streptococcus, was 61.7 per cent, while in empyema, due to the pneumococcus, the mortality was 45 per cent.

TABLE 10—MORTALITY OF EMPYEMA AS TO TYPE OF INFECTION

	Streptococcus			Pneumococcus		
	Total	Deaths	Per Cent	Total	Deaths	Per Cent
Lobar pneumonia	77	45	58.4	32	11	34.3
Measles pneumonia	38	26	68.4	8	7	87.5
Total	115	71	61.7	40	18	45.0

2 The method followed was that of the Rockefeller Institute mouse injection until Jan 10, 1918, since when Avery's synthetic medium has been used. Until about March 15, 1918, a gram stain, a subculture in plain broth and on blood agar plate was made from the Avery medium culture. Since that date the subculture in broth has been discontinued. The precipitin method was used for a long period, but the agglutination method was found to be preferable and compulsory, of course, when bile was not available. In the differentiation of pneumococcus Type IV from the streptococcus, the bile test and the cultural characteristics on the blood agar plate were used.

DISCUSSION

The hemolytic streptococcus and the mixed group, pneumococcus Type IV and nonhemolytic streptococcus, were the organisms found in the sputum in 67.4 per cent of 428 instances of completed pneumonia cases in this hospital. The streptococcus was the organism found in 74.2 per cent of 155 instances of empyema. In January it

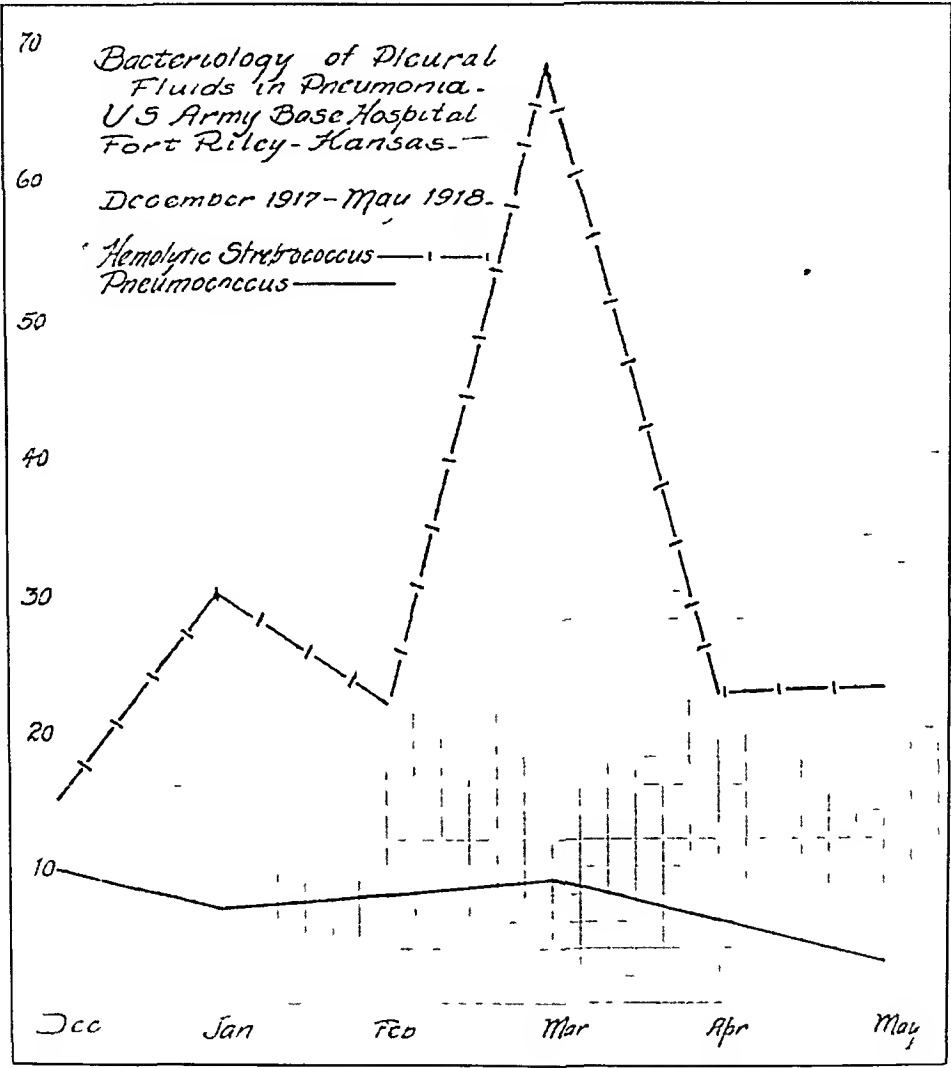


Fig 5—Curves showing the incidence of types of bacteria in pleural fluids in pneumonia

was noticed, in a study of the sputum curve in the laboratory, for all sputa sent in, that Type II pneumococcus, including the atypical Type II, began to parallel the curve of the Type IV pneumococcus. In March the apexes of the curves for these types and the hemolytic streptococcus reached their height. It was during March that an influx of severe lobar pneumonia with frequent empyemas occurred.

The rapid occurrence, in these cases, of empyema, due to hemolytic streptococci, with rapid reaccumulation of fluid despite daily aspirations of quantities varying from 500 to 1,800 c c, with death within a week and at necropsy a collapsed lung on the affected side, led us to believe that a combination or double infection had occurred. This condition was responsible for the greatly increased death rate in March and occurred in epidemic form (Figs 4 and 5).

Since Type II pneumococcus is not strictly a "fixed" type and the Type IV pneumococcus is not "fixed" at all, it appears that an association exists between these groups and the hemolytic streptococcus, and that a closer study of the relationship of the hemolytic streptococcus to Types II and IV pneumococcus is highly desirable. Very few of the infections have been due to the nonhemolytic streptococcus.



Fig 6—Diagnosis, walled off fluid, right side. After four aspirations of decreasing quantities of pus the patient recovered without operation.

It has been noteworthy that so many hemolytic streptococcic empyemas have occurred in pneumonia patients, in which pneumococcus Type IV was reported in the sputum—22 of 72 instances, or 30 per cent. Bile solubility tests were not made in all of these instances, but the inference may be made that the pneumococcus, Type IV, predisposed to infection with the hemolytic streptococcus as a secondary invader. On the other hand, in 45 of 72 instances (62.5 per cent) of streptococcic empyema, the sputum examination revealed streptococci. In other words, 92.5 per cent of 72 streptococcic empyemas had either streptococcus or pneumococcus, Type IV, in the sputum. In 40 pneumococcus empyemas the sputum showed hemolytic streptococci in 5, nonhemolytic streptococci in 1, and pneumococcus, Type IV, in 15. In other words, 52.5 per cent of 40 pneumococcus empyemas had either streptococcus or pneumococcus, Type IV, in the sputum.

Throat cultures were taken of lobar pneumonia patients several days after admission in fifty-nine instances. Thirty of these, or 50 per cent, showed hemolytic streptococci. An order was issued at this time requiring that all milk be boiled before use and prohibiting the use of uncooked cheese. Since that time throat cultures were made in eighty-one instances of lobar pneumonia on admission to the wards. It was found that 17 per cent of these patients had hemolytic streptococci on admission. This number did not show an increase for cultures taken five and six days later. Data on throat cultures of measles patients, on admission and subsequently, are too incomplete for publication at this time.



Fig 7—Diagnosis, pericardial effusion. Recovered after aspiration.

PATHOLOGY

The basis of study in this series is founded on 153 necropsies, of which 107 (70 per cent) were instances of lobar pneumonia and 46 (30 per cent) were measles pneumonia. Included among the instances of measles pneumonia were 19 cases of lobar (41 per cent) and 25 cases of bronchopneumonia (54 per cent).

Particular interest is attached to the consideration of pneumonia following measles. In the early stage of lobular or bronchopneumonia the lungs were congested, edematous and crepitant, although on cut section little air could be expressed. Depending on the extent of lobular consolidation, light areas alternated with darker areas of infiltration, which darker areas corresponded on the pleural surface to blue-gray areas of collapse. The appearance was that of extensive lobular consolidation through the confluence of which more extensive involvement of portions of lobes occurred. Between these areas of lobular consolidation were noncollapsed air-containing portions, although these were much less prominent in number and appearance than the darker consolidated areas. Hemolytic streptococci were obtained in many instances from the lungs at necropsy.

Cole and MacCallum³ have recently called attention to the interstitial type of pneumonia observed by them at the base hospital, Fort Sam Houston, Texas. The interstitial type in their cases was common after measles and was due to the streptococcus. On cut section the lungs showed prominent gray solid peribronchial nodules, with a shotlike feel to the fingers, due to edema, hemorrhages, organization and induration. Fibrinous plugs were found in the alveoli, while the alveolar walls were infiltrated with mononuclear cells. Few streptococci were found in the lungs, but large numbers were found in the pleural exudate. These streptococci were believed to be of low virulence, evidenced by absence of spread throughout the body.



Fig. 8—Diagnosis, purulent pericarditis, adhesive mediastinitis

MacCallum found that lobular pneumonia also followed measles, due to an overwhelming streptococcus infection. In this type, patchy hemorrhagic areas of consolidation were present, containing large numbers of streptococci. The alveoli contained an exudation of polymorphonuclear cells and often was associated with necrotic areas in the lungs.

It is undoubtedly true that pneumonia of the interstitial type frequently follows measles. We have seen many such instances, but we have likewise frequently encountered this type of involvement not associated with measles. We believe that in these streptococcic pneumonias the difference between the interstitial and the lobular types is one of degree rather than kind. The interstitial type with partially plugged bronchioles and peribronchiolitis leading to small nodular

³ Cole, Rufus and MacCallum, W. G. Jour. Amer. Med. Assn., 1918, 70, 1146

consolidations occupying portions of a lobule, may at a later stage, due to confluence of such areas, involve neighboring bronchioles and present the picture of an extensive lobular pneumonia. Different stages of the process have been frequently seen to occur in the same lung. Microscopically,⁴ in the interstitial type, the bronchioles were filled with leukocytes to the point of occlusion. The tissue surrounding the cut bronchiole was infiltrated with mononuclear cells. The walls of neighboring alveoli contained fewer mononuclear cells, polymorphonuclear cells and connective tissue cells with spindle-shaped nuclei. In the alveoli were many red blood cells and polymorphonuclear cells. In the more extensively consolidated portions of the



Fig 9—Diagnosis, free fluid, right side, upright position

same lung, due to confluence of lobules, large mononuclear (wandering tissue) cells were found with many leukocytes and red blood cells.

In this series, the incidence of extension to serous membranes in lobar and bronchopneumonia shows but little difference (Table 11)

TABLE 11—NECROPSY INCIDENCE

	Lobar Pneumonia,* Per Cent	Bronchopneumonia, Per Cent
Empyema	23.4	24.0
Peritonitis	3.0	2.8
Purulent pericarditis	2.5	1.7
Subcostosternal pus pockets	3.4	3.3

* Including lobar pneumonia following measles

The hemolytic streptococcus was the organism most commonly found in these extensive complications, whether in lobar pneumonia or measles pneumonia.

4 We are indebted to Prof. A. S. Warthin of the Department of Pathology, University of Michigan, for the preparation of microscopic specimens and photomicrographs.

Pulmonary embolus involving the left branch of the pulmonary artery, because it is the straight branch, occurred in two instances. In both, thrombosis had occurred in the hemorrhoidal and prostatic plexus, involving the right hypogastric vein and extending into the inferior vena cava, from which a detached portion of the thrombus had been carried to the right side of the heart. The right hypogastric vein passes under the right external iliac artery at the brim of the pelvis, which makes a thrombosis more apt to occur in this locality. On the left side, the vein parallels the artery.

Except for a series of twenty-six multiple pulmonary abscesses, which were more frequently met with during a rapidly progressive type of streptococcic infection in lobar pneumonia in March, pulmonary abscess was not a frequent complication. These occurred in

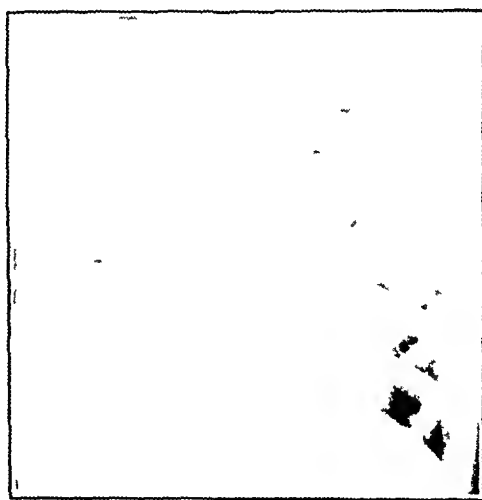


Fig 10—Diagnosis, thickening of interlobar pleura, right side. Small quantities of pus aspirated twice. Patient recovered without operation.

lobar pneumonia when a streptococcic infection had apparently been superimposed on the lobar pneumonia. In view of the great number of thoracenteses made in diagnosing empyema, and in the daily aspirations, the relative infrequency of pulmonary abscess leads us to discount the common belief that there is any appreciable amount of danger in performing pleural punctures, due to the possibility of lung puncture and subsequent abscess formation.

Miliary tuberculosis was found at necropsy in seven instances presenting the symptoms of bronchopneumonia. The diagnosis was made in three of these patients prior to death. One instance of syphilitic interstitial pneumonia of rapid progress simulating bronchopneumonia was not diagnosed prior to necropsy.

GENERAL PLAN OF TREATMENT

It was possible to have separate dressing and operating rooms in the separate buildings given over to the care of lobar pneumonia and measles pneumonia. These were of great service in securing protection from the contagion of measles in the lobar pneumonia patients. One ward in each pneumonia section was set aside as a receiving ward. In this ward the first examination was made and the diagnosis established. The specimen of sputum for determination of the type of pneumococcus in lobar pneumonia was collected, whenever possible, in this ward. In the measles pneumonia receiving ward a throat swab was made for streptococcus culture.⁵ Measles streptococcus carriers are now segregated from nonstreptococcal measles patients. Fresh air wards were utilized in the open air treatment of all serious cases.



Fig 11—Diagnosis, lobar pneumonia, right upper lobe

In the other pneumonia wards, each patient was given approximately 1,000 cubic feet of air space.

During the first forty-eight hours after admission it was the plan of the medical service in the base hospital, since Jan 15, 1918, to digitalize all pneumonia patients. The tincture of digitalis was used. Each batch of digitalis tincture was standardized according to the cat method of Hatcher,⁶ as amplified clinically by Eggleston.⁷ The estimated amount necessary to secure effect, according to body weight, was administered in doses of 2 c c to 4 c c every four hours until the total dosage had been given. Its use in this manner to prevent cardiac

5 A throat swab for culture of streptococcus is made on all measles patients on admission.

6 Hatcher, Robert A., and Brody, J. G. *Am Jour Pharm*, 1910, **82**, 360.

7 Eggleston, Cary. *ARCHIVES INT MED*, 1915 **16**, 1. We are indebted to Dr. Cary Eggleston of Cornell Medical College, N. Y., for numerous standardizations of digitalis tincture.

failure has been beneficial. The average tincture which we have used was standardized to a dosage of 0.17 c c per pound of body weight of patient. If the patient had not within a week had any form of digitalis, the following average total dosage was used:

For 120 pounds body weight—20 c c in divided doses
For 130 pounds body weight—22 c c in divided doses
For 140 pounds body weight—24 c c in divided doses
For 150 pounds body weight—26 c c in divided doses
For 160 pounds body weight—28 c c in divided doses
For 170 pounds body weight—30 c c in divided doses

Patients rarely vomited from the effects of digitalis administered in this manner. If the dosage should be carried further, to affect the vomiting center in the medulla, vomiting may occur. In the hundreds



Fig. 12—Diagnosis, lobar pneumonia of right upper and middle lobes

of patients treated with digitalis at this hospital, vomiting occurred from the effects of the drug in not more than four or five instances. We have seen but one instance of partial heart block, of temporary duration, which could be attributed to it. In only one instance have we seen a considerable rise of blood pressure (to 190) following its administration. The general circulatory effects were beneficial in sustaining the heart in pneumonia for the stress placed on it during an acute illness of such severity.⁸ For intravenous emergency digitalis therapy, after the patient had received his total dosage of the tincture as outlined, we depended, when obtainable, on digipuratum. Digitalone, two $\frac{1}{10}$ -grain tablets dissolved in 15 to 30 minims of sterile water, was also used intravenously for similar purpose. For emergency use orally, we also used Nativelle's crystalline digitaline. In the

⁸ The tincture of digitalis was made from Allen's leaves with 75 per cent alcohol instead of the 50 per cent alcohol prescribed by the U. S. P.

following tabulation is shown the proportion of deaths not associated with sepsis, and which may be attributed to circulatory failure for the predigitalis period and the digitalis period

Predigitalis Period, October 18 to January 15		Per Cent
Deaths not associated with sepsis		25.8
In lobar pneumonia		17.1
In measles pneumonia		46.3
Digitalis Period, January 15 to May 18		
Deaths not associated with sepsis		11.8
In lobar pneumonia		11.2
In measles pneumonia		14.8

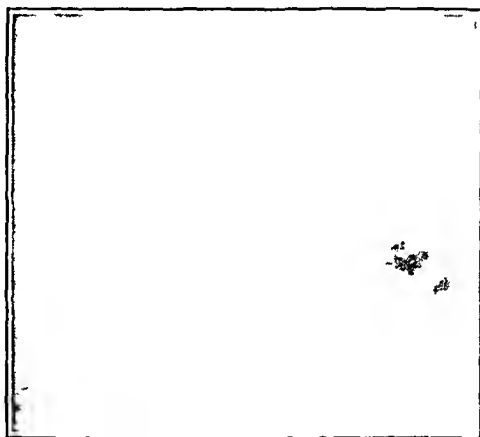


Fig 13—Diagnosis, left pyopneumothorax with adhesions to the parietal pleura. The patient died several days later with double empyema, multiple abscesses in left lung and endocarditis

Pituitary extract was used on two indications—falling blood pressure and tympanitic abdominal distention. It was administered intravenously and intramuscularly. If the distention is due to paralytic ileus, pituitary extract may be of benefit because of its effect on involuntary muscle tissue in stimulating peristalsis. If, however, as mentioned, the distention is the result of spastic ileus, pituitary extract would be contra-indicated, and hot abdominal packs, a starch and opium enema, an opium and belladonna suppository, or a physiologic dose of atropin ($\frac{1}{75}$ to $\frac{1}{60}$ grain) should be used instead. Careless use of the rectal tube or frequent irritating enemas may produce thrombosis in the inferior and middle hemorrhoidal veins with extension to the hypogastric vein (right) leading to the possible occurrence of pulmonary embolism. Caffein and sodium benzoate or coffee was used as a general stimulant, morphin was used for restlessness. Veronal or trional was contraindicated. Atropin in doses of $\frac{1}{100}$ grain three times a day was of value in the treatment of pulmonary edema or bronchorrhea incident to bronchopneumonia.

SERUM THERAPY

Cole Type I serum was administered in doses of 100 c c intravenously after desensitization in Type I lobar pneumonias⁹ Its effect was, in a large percentage of cases, immediately beneficial Within twelve to twenty-four hours the temperature would in some instances drop by crisis to normal The dose was repeated daily for three or four days when indicated There were thirty-two Type I pneumonias Death occurred in five One of these patients had pneumococcic otitis media and diffuse pneumococcic meningitis at necropsy, from one other patient meningococci and pneumococci were obtained by spinal puncture repeatedly before death from meningitis, while two more deaths were due to bilateral empyema The mortality, including these four complications, was 15.6 per cent Cole Type I serum was admin-



Fig. 14—Diagnosis, left pyopneumothorax with adhesions to parietal pleura

istered in twenty-seven of the thirty-two cases Among those who received the serum there were four deaths (two had meningitis and one had bilateral empyema mentioned above) The mortality in the serum treated patients was therefore 14.8 per cent

The autolyzed pneumococcic antigen of Rosenow was used in seventy patients with lobar pneumonia not due to Type I pneumococcus Table 12 shows the day of the disease when the antigen was first administered, the number of empyemas and the mortality

Among 219 completed instances of lobar pneumonia in which the patients were discharged during the same period and not treated with the antigen, the mortality was 14.6 per cent In many instances fol-

⁹ Desensitization was carried out as follows 0.5 c c subcutaneously followed in one hour by 10 c c subcutaneously One hour later the serum was administered intravenously

lowing the administration of the antigen the temperature fell abruptly by crisis after one or two doses. It is our belief, although no great differences in the mortality were affected by its use during the same

TABLE 12—COMPLICATED CASES LOBAR PNEUMONIA TREATED WITH AUTOLYZED PNEUMOCOCCIC ANTIGEN¹⁰

Begun on	Number of Patients	Recoveries	Deaths	Empyemas *
1st day	22	14	4	4
2nd day	26	20	3	3
3d day	8	6		2
4th day	6	6		
5th day	2	2		
6th day	2	1		1
7th day	1		1	
8th day	2		1	1
10th day	1	1		
Total	70	50	9*	11†

* Mortality 12.8 per cent. Incidence of empyema 15.7 per cent.

† Empyema patients still in hospital, May 18, 1918.



Fig. 15—Diagnosis, right pneumothorax, left upper, resolving pneumonia. Following a severe attack of coughing the patient suddenly became extremely dyspneic and cyanotic and showed signs of a spontaneous, complete right pneumothorax, which was later confirmed by roentgenogram. There was gradual but complete recovery.

period when the antigen was not used in corresponding cases, that the duration of the disease was shortened. The results were gratifying in many instances. We shall continue its use. The dosage, 1 to 2 c.c. daily subcutaneously for four or five doses, produces practically no reaction. We believe, however, that the Cole Type I serum should be used in Type I cases.

¹⁰ Dr. Rosenow has kindly prepared for us an antigen containing a large fraction of our local strains of pneumococci which will be used in the treatment of pneumonia patients.

Through the kindness of Dr Preston Kyes of the University of Chicago we were enabled to use his antipneumococcic chicken serum in thirty cases of lobar pneumonia due to the pneumococcus. One death occurred, a mortality of 3.3 per cent, with an empyema incidence of 13.3 per cent. During the corresponding period the mortality of lobar pneumonia in patients not treated with this serum was 14.2 per cent. The serum seemed to possess value in reducing the toxemia in pneumonia, but in a few instances, after desensitization, the intravenous administration produced severe reactions, with high temperature. These reactions have been entirely absent in recent batches of serum. Its value as a curative agent, judging from this small series of cases, is undetermined.

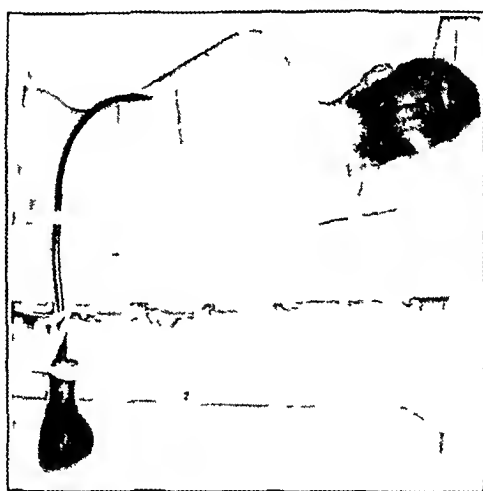


Fig 16—Brewer tube and Ewald bulb as used for suction drainage in empyema

MEASLES PNEUMONIA

Measles patients received, since Feb 15, 1918, a vaccine prepared from five local strains of streptococci and two strains of *Pneumococcus* IV, on the first, fourth and eighth days after admission. The incidence of measles pneumonia from October to February 15, prior to the use of the prophylactic vaccine, was 6 per cent. The incidence of measles pneumonia from February 15 to May 18 in 148 cases in which the prophylactic vaccine was used was 2 per cent. But one patient died of pneumonia in this latter series.

We have used antistreptococcus serum intravenously, after desensitization, in measles pneumonia due to the streptococcus with beneficial results in many instances. Agglutination tests of the local strains of streptococci encountered were made with stock serums, and it was found that agglutination occurred in dilutions of from 1 to 40 to 1 to 80 with a majority of the strains. The dosage was 50 c c intravenously, repeated daily for three or four doses.

THE TREATMENT OF EMPYEMA¹¹

The total number of empyema complications following pneumonia in this series was 200. Of this number 119 men were operated on, all but a few of the earlier cases by Major Phillips, eighty-one men were not operated on. This latter group was made up of those patients who were not considered reasonable operative risks, or in whom the condition was not diagnosed prior to necropsy.

TABLE 13—TYPE OF OPERATION FOR EMPYEMA

	Number	Mortality, Per Cent
Rib resection	76	48.6
Thoracotomy	43	53.5
Right side	70	47.1
Left side	49	55.1

Fifty-nine per cent of the empyemas occurred on the right side, 41 per cent on the left side. Local anesthesia has been the method of choice, having been used in 85 per cent of the operations.

TABLE 14—ANESTHESIA IN EMPYEMA OPERATIONS

	Number	Mortality, Per Cent
Local	102	50
General	17	53

If the plan is followed of early aspirations and late operations, mentioned later, the operation may be performed under ether anesthesia with comparatively little risk. We believe, however, that local anesthesia and nitrous oxid oxygen anesthesia are the methods of choice.

DISCUSSION

For the period October 18 to January 29, early operation was performed on all empyemas. During this period 83 patients were operated on, of whom 52 died, a mortality of 63.8 per cent. It has been possible, in Army hospitals, where the patients are under complete control from the beginning of their illnesses, to diagnose empyema earlier than has been possible in civil life. For the period mentioned in which early operation was performed the presence of pus containing organisms was considered to be a sufficient indication.

Beginning on January 12 the medical treatment of this condition was changed in several particulars as follows. As soon as the diagnosis of empyema was made during the course of pneumonia, aspiration,

¹¹ May 18 there were under treatment 182 patients with pneumonia, among whom there were forty-six instances of empyema in which operation was performed.

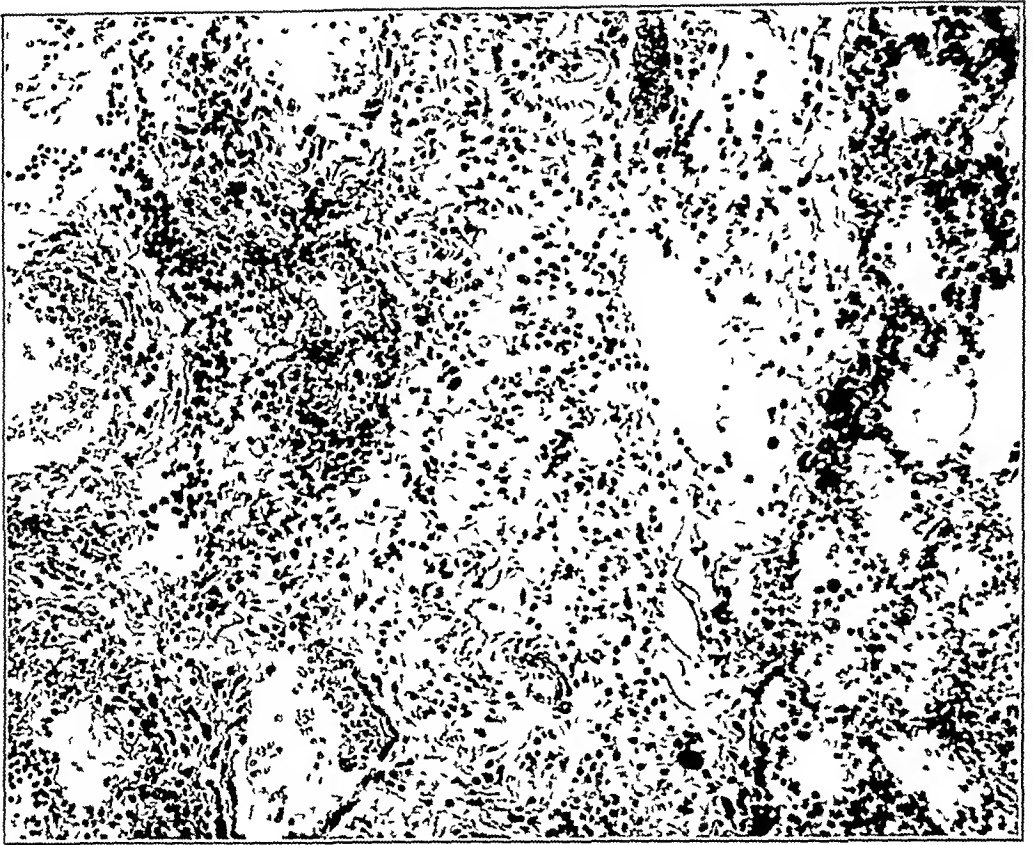


Fig 17—Bilateral streptococcus lobular pneumonia following measles Early stage peribronchial infiltration, leukocytes in cut bronchioles, mononuclear cell infiltration in walls of alveoli



Fig 18 —Bilateral streptococcus lobular pneumonia following measles Occlusion of alveoli with plugs of fibrin and cellular debris

using the Potain apparatus, was done, as a rule, every alternate day. This was continued until the pus became too thick for aspiration—for twelve to fifteen days. When the pneumonic process had subsided the advisability of operation was considered. If the pus became too thick for aspiration and it was not considered that the patient's condition warranted operation, intrapleural lavage was practiced at the time of aspiration, in closed circuit, by connecting a bottle containing warm saline solution to the aspirating tubing. In this manner thick



Fig 19—Bilateral streptococcus lobular pneumonia following measles, the cut bronchiole filled with leukocytes, the tissue surrounding shows mononuclear cell infiltration. The lungs showed air containing tissue in many areas.

pus could be diluted sufficiently to permit aspiration. Care was taken at the time of all aspirations, whether with the syringe or with the Potain apparatus, to prevent collapse of the lung by admission of air. The operation was not performed until twelve to twenty days had elapsed. The clinical judgment of two or three physicians, who followed the course of the infection from day to day, was utilized in deciding the best time for operation.

In all, eleven patients recovered by repeated aspirations without operation. The number of aspirations in these patients varied from one to ten. In one of these an aggregate of 835 cc of pus were removed by five aspirations, in another 7,660 cc of pus were removed

by eight aspirations, while in another 635 c.c. of pus were removed by ten aspirations. In five of the eleven the empyema was due to hemolytic streptococci, in one, to pneumococcus Type II, in one, to pneumococcus Type III, and in two, to pneumococcus Type IV. In one, the type of pneumococcus was not determined. Of these eleven empyemas, nine followed lobar pneumonia and two followed measles pneumonia.

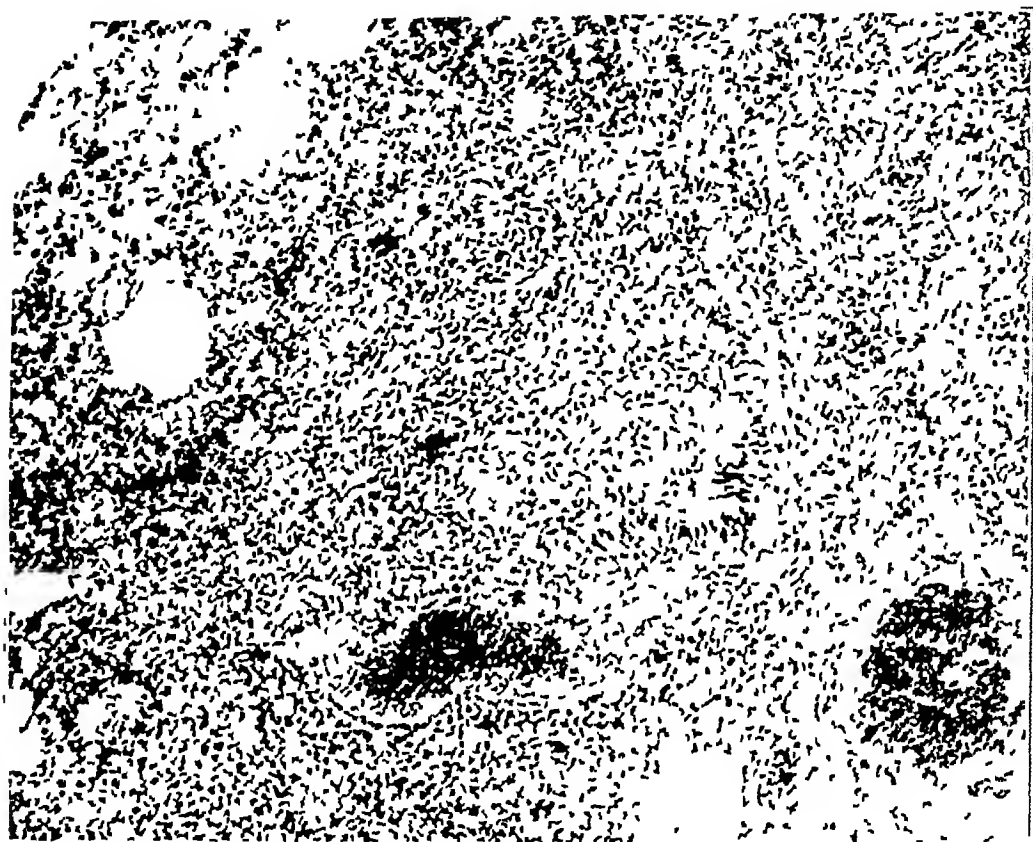


Fig. 20—Bilateral streptococcus lobular pneumonia following measles with localized abscess formation

At the time of operation the Brewer tube was preferred, to which was attached a partially collapsed Ewald bulb (Fig. 16). Negative pressure and suction were readily obtained in this manner. The tube was clamped and the bulb emptied whenever the patient complained of pain in the chest. In all of the earlier operations the ordinary rubber drainage tube was used and was latterly used when it seemed more suitable in order to reach a pocketed area of pus, such as an interlobar empyema. Since January 12 neutral solution of chlorinated soda (Dakin's solution) has been used for the daily irrigation of empyema wounds. There was a marked decrease in the odor and the amount of discharge was lessened in many instances. Operations were

begun, after preliminary aspirations as outlined, on January 29 The comparative results for the two periods are shown in Table 15

TABLE 15 —OPERATIVE MORTALITY IN 119 COMPLETED CASES OF EMPYEMA

	Number	Deaths	Mortality, Per Cent
Early operations not preceded by repeated aspirations (October 18 to January 29)	83	52	63.8
Late operations preceded by repeated aspirations (January 29 to May 18)	36	8	22.2

There were, on May 18, 46 operated empyema patients in the hospital, of whom 44 were classified under late operations. Of these 44 patients, the prognosis was considered favorable in 38 and unfavorable in 7. If these patients are added to the foregoing list of late operations, for purpose of comparison and to sustain our argument for the late operation the mortality will, according to present judgment, be expressed as shown in Table 16¹²

TABLE 16 —MORTALITY AFTER LATE EMPYEMA OPERATIONS

	Number	Deaths	Mortality, Per Cent
Late operation preceded by repeated aspirations (January 29 to May 18)	80	15	18.7

These tables have been particularly interesting to us in view of the fact that the mortality of pneumonia with operated empyema, by this plan of treatment, has been reduced to a point not much higher than pneumonia without empyema.

TABLE 17 —COMPARATIVE MORTALITY IN EMPYEMA

	Number	Deaths	Mortality Per Cent
Pneumonia with empyema, nonoperated	81	70	86.4
Pneumonia with empyema, early operation	83	52	63.8
Pneumonia with empyema, late operation	36	8	22.2
Pneumonia without empyema	671	109	16.2
Total	871	239	27.4

Sept. 25, 1918, the completed figures were as follows:

	Number	Deaths	Mortality, Per Cent
Late operation preceded by repeated aspiration	80	13	16.2

On September 25 the completed figures for the early operation were as follows:

	Number	Deaths	Mortality, Per Cent
Early operations <i>not</i> preceded by repeated aspirations	85	52	61.2

¹² The mortality has been decreased since this table was completed in May

For about two months the injection of stock antiserum (pneumococcic and streptococcic) in quantities of 75 to 100 c c, was made intrapleurally after repeated aspirations. We could find no evidence that this was of decided benefit.

CONCLUSIONS

1 The mortality in pneumonia in this series of cases, observed over a period of seven months, varies from month to month with the type of infection.

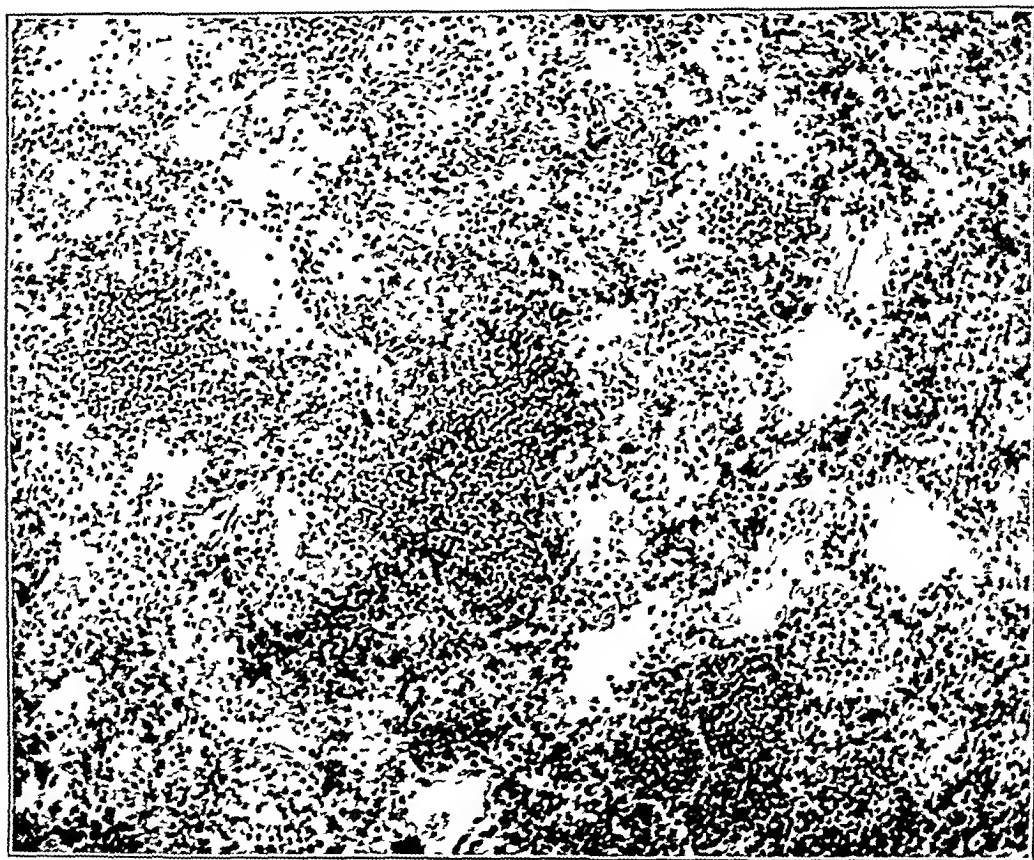


Fig 21—Bilateral streptococcus lobular pneumonia following measles. The patchy areas of consolidation are seen, many alveoli contain red blood cells and polymorphonuclear cells.

2 The mortality in measles pneumonia is approximately twice as high as lobar pneumonia. Interstitial pneumonia is believed pathologically to be an early stage of lobular bronchopneumonia. In both, streptococci were the predominating organisms. In the interstitial type death may occur before the process has extended sufficiently to produce extensive consolidation, through the confluence of lobules, and the condition be recognized pathologically as bronchopneumonia.

3 The use of a standardized tincture of digitalis, in sufficient dosage to produce physiologic effect, is believed to be responsible for



Fig 22 — Bilateral streptococcus bronchopneumonia following measles
Bronchus filled with purulent exudate, beginning suppuration of wall

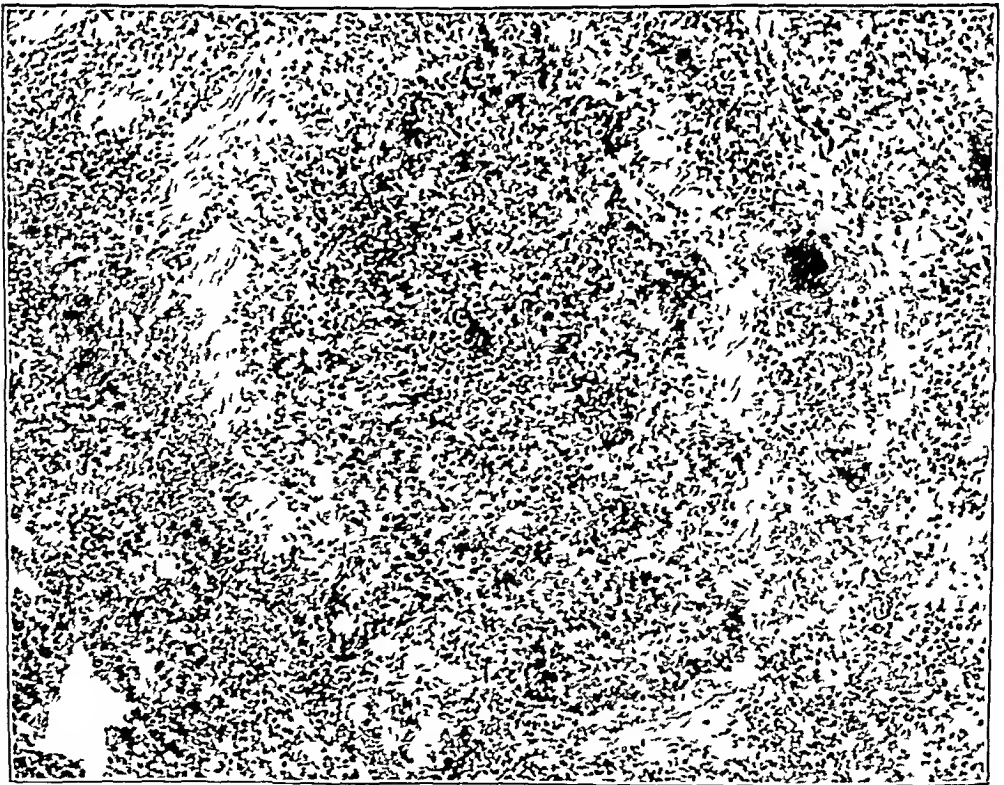


Fig 23 — Bilateral streptococcus bronchopneumonia following measles
Bronchus with complete destruction of epithelium filled with pus in the middle
of an atelectatic area

a decrease of deaths in this series not associated with empyema or other septic complications, that is, the deaths which are associated with cardiac failure

4 Empyema occurred in 23 per cent of 871 instances of pneumonia and was responsible for 54.3 per cent of the deaths

5 Early diagnosis of empyema is essential. Repeated aspirations, as described in the foregoing, for from twelve to fifteen days, followed by late operation, has reduced the mortality from 61.2 per cent to 16.2 per cent.¹²

6 The mortality of streptococcus empyema in relation to the mortality of pneumococcus empyema is approximately that of a ratio of 3 to 2

7 Empyema patients should be retained in the medical service after operation. The surgeon assigned to the medical service for this work should spend his time in the pneumonia wards for this special duty. Complications such as extension of pneumonia to the opposite side, or reinfection of the affected lung, are recognized more promptly by the physicians of the medical service who have observed the patient from the outset

8 The necropsies of this series have shown in many instances purulent accumulations beneath the sternum, which may be designated subcostosternal pus pockets. Infection apparently reaches this inaccessible location by way of the parietal lymphatics leading to substernal lymph nodes. The diagnosis of this condition can, as a rule, only be made at necropsy. Drainage of these pockets offers great difficulty. Extension to the pericardium frequently occurs in connection with these pus pockets

9 The relationship of pneumococcus, Types II and IV, to hemolytic streptococci of high virulence deserves further study

10 Cole Type I serum should be used in Type I lobar pneumonia. Rosenow's autolyzed pneumococcic antigen and Kyes' antiserum have been of apparent benefit in the treatment of lobar pneumonia

11 A prophylactic vaccine administered to measles patients has appeared to possess some value, when administered on the first, fourth and eighth days after admission, in the prevention of pneumonia

PNEUMONIA AND EMPYEMA AT CAMP SEVIER

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Recent rather numerous reports from the various army camps throughout the country concerning the incidence and causative agent of pneumonia, during the last winter, have mentioned frequent infection with *Streptococcus hemolyticus* and less frequent occurrence of pneumococcus infection. Reports from the different camps would indicate that the predominating organism is not the same in all localities. In Camps Funston, Dodge, Custer and Lee hemolytic streptococcus has been reported as the prevailing organism. At Camps Wheeler, Beauregard, Hancock, Jackson, Logan, Sheridan and Travis more pneumococcus infections are reported.

In the findings so far published attention has been directed chiefly to the study of bronchopneumonia and, more especially, empyema. There has been very little comparative study of lobar and bronchopneumonia. The studies of the commission headed by Cole and McCallum¹ at Fort Sam Houston, have been made with this point in view and their results would indicate that the true lobar pneumonia is now, as formerly, a pneumococcus infection, whereas the bronchopneumonia, or postmeasles pneumonia, is predominantly streptococcic. In certain other camps these postmeasles pneumonias and empyemas are reported as being frequently pneumococcic.

The present report has been undertaken in an attempt to present a comparative study of lobar pneumonia and bronchopneumonia as they have occurred at Camp Sevier and to draw conclusions regarding the type of infection and the complications that have arisen. Five hundred and sixty-seven cases of pneumonia were admitted to the base hospital prior to March 31, 1918. This group divides itself into 234 lobar pneumonia and 333 bronchopneumonia patients. Those cases which have occurred subsequent to March 31, during the preparation of this report, are not incorporated in the accompanying statistical review, but several showing unusual features have been included in the discussion.

1 Cole, Rufus, and McCallum, W G. Pneumonia at a Base Hospital, Jour Am Med Assn, 1918, **70**, 1146

INCIDENCE

Of 9,650 admissions to the Base Hospital, 24 per cent were for lobar pneumonia, and 34 per cent for bronchopneumonia. In Chart 1 is shown the total number of lobar cases in the hospital on each day from Nov 23, 1917, until May 1, 1918. During the latter part of December and during the months of January and February there was a high incidence of the disease, there being on February 3 as many as seventy-six cases. As shown by the weather notes in Chart 2 the steady increase during the month of January was during a period of very inclement weather and, following the onset of pleasant weather about February 6, there occurred on February 15 a decided fall in the curve which persisted throughout the remaining period. In April there were two other rises in the curve. The first followed by a few days a parade in which the soldiers had all become rain-soaked. At this time also a mild epidemic of influenza occurred which persisted for two or three weeks. The second rise in the April curve accompanied an increase in the influenza. These postinfluenzal pneumonias were chiefly lobar in type, although a few were bronchopneumonias, and they were all unusually sick. The incidence of empyema in this later series was also much higher than in the series up to March 31, being as high as 50 per cent.

In regard to the incidence of bronchopneumonia, this camp was comparatively free from disease during the month of September and the first weeks of October, 1917. With the influx of 8,000 draft men, there was then inaugurated a division wide epidemic of measles. Many of the new men coming from other camps had the measles rash on arrival, and others had only recently been in communities where the disease was endemic. As a result, 3,520 cases, or 12.8 per cent, of the entire strength developed in the division. One thousand and twenty-nine patients were in the base hospital at some time of their illness. Of the 333 cases of bronchopneumonia which soon developed, 292 were very definitely postmeasles.

In Chart 3 the morbidity curves of bronchopneumonia and measles show not only the correspondence between the two diseases, the bronchopneumonia lagging somewhat behind the measles, but the chart also shows, especially in the month of January, the absence of relationship between the bronchopneumonia incidence and that of lobar pneumonia as seen in Chart 1. As a discussion of the clinical records will show, lobar pneumonia was a complication of measles only in a small number of cases and was on the whole a primary affection. Chart 3 also indicates that with the onset of pleasant weather in February and at a time when more effectual quarantine and isolation were in effect in the camp and in the hospital, respectively, bronchopneumonia followed

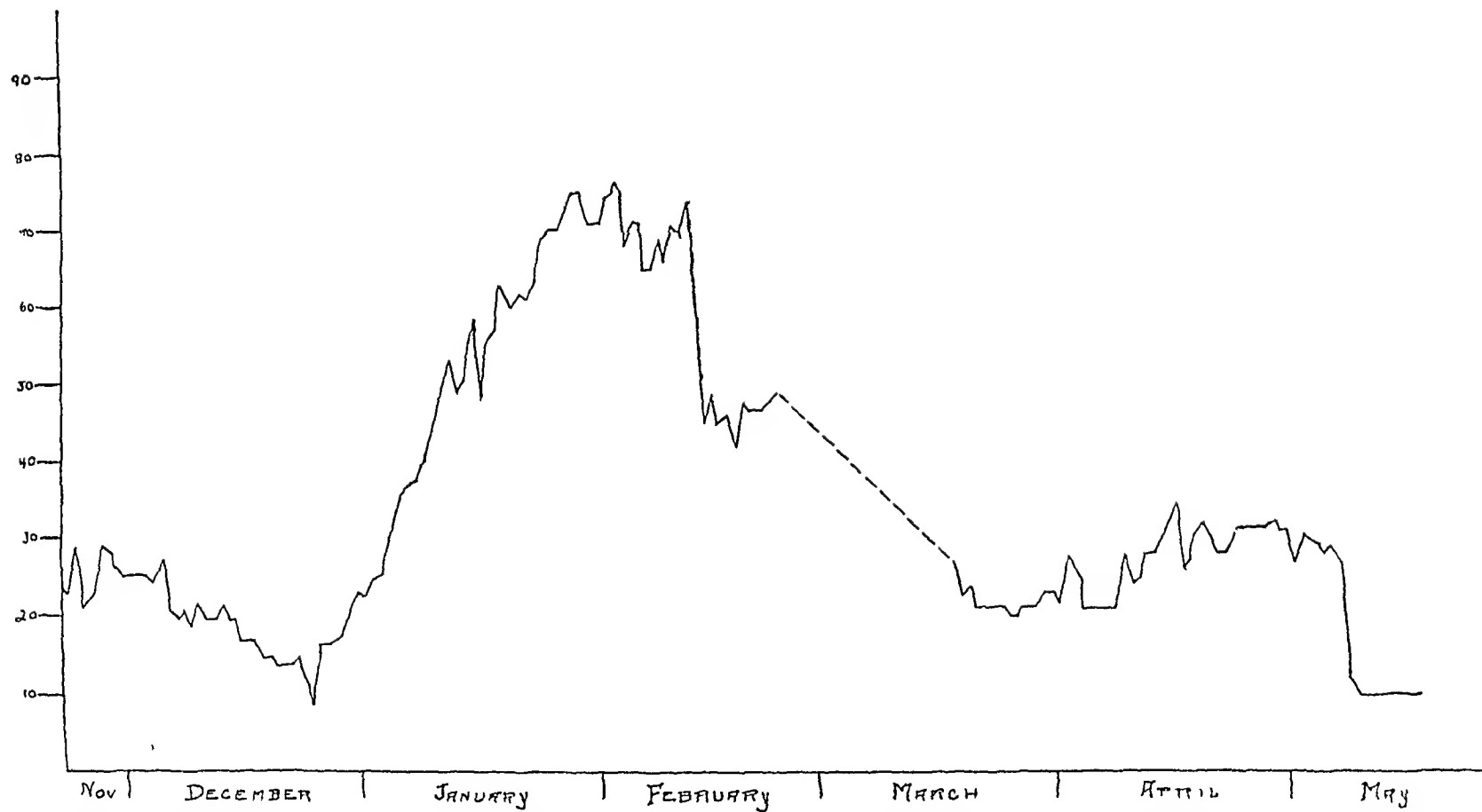


Chart 1—Showing the number of lobar pneumonia cases in the hospital from Nov 23, 1917, until May 1, 1918 The highest incidence of the disease occurred on February 3, when seventy-six patients were in the hospital

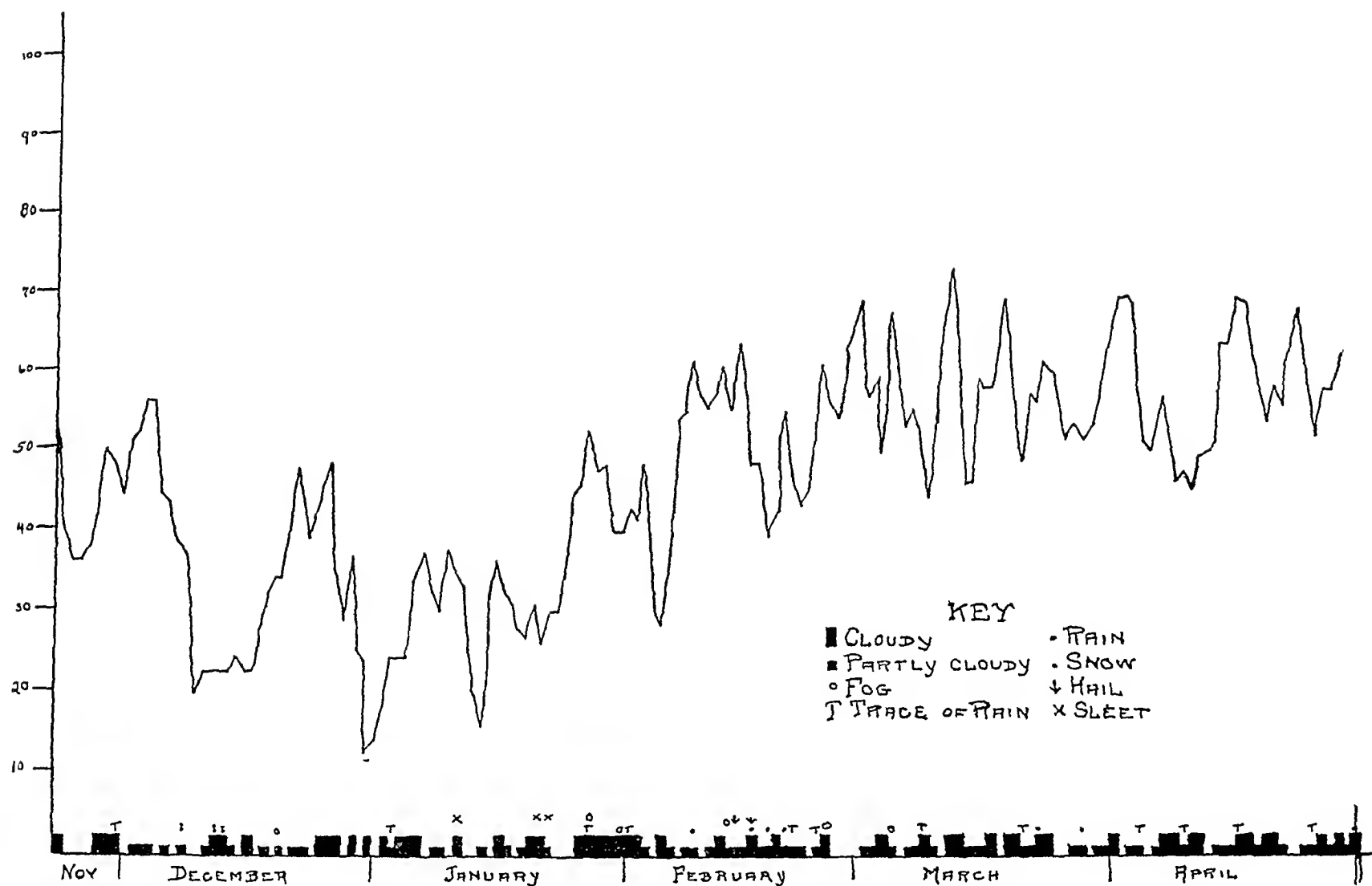


Chart 2—Weather chart giving the temperature curves and data regarding the weather during the time the pneumonia cases described in this article occurred. As recorded by the chart there was a high incidence of the infection during the stormy periods.

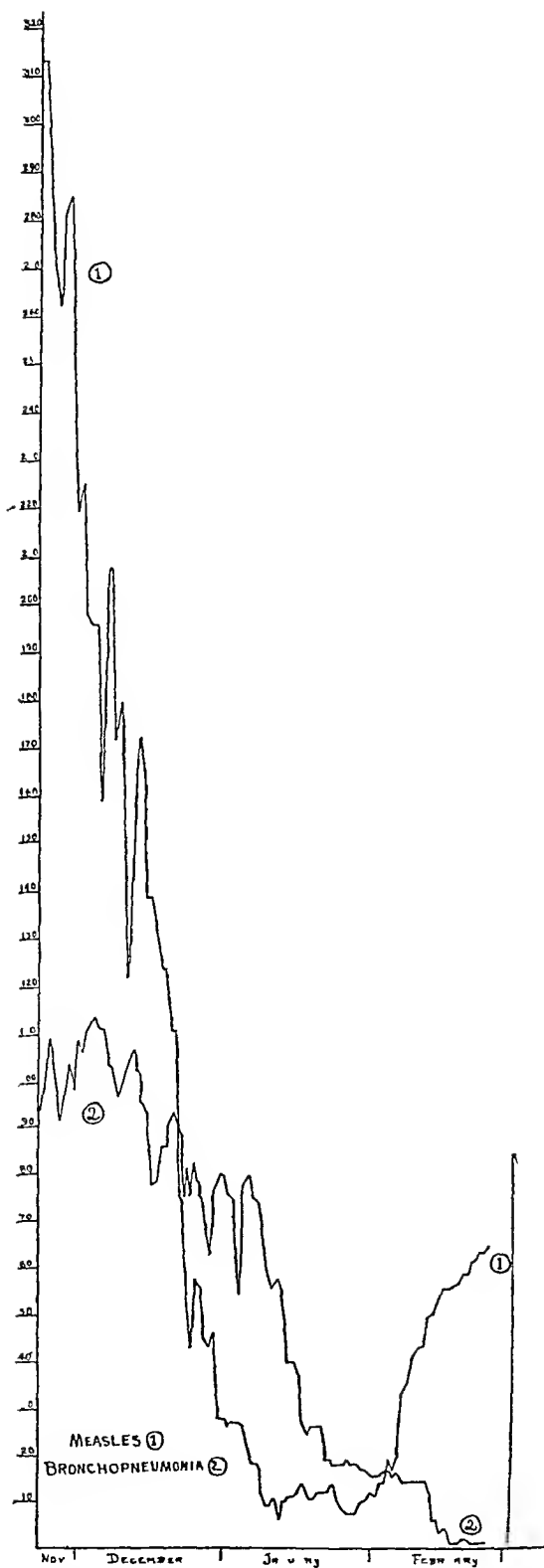


Chart 3—Morbidity curves of the measles and bronchopneumonia cases which show the relationship between these diseases. The bronchopneumonia cases lagged somewhat behind the measles epidemic.

measles in a decidedly smaller number of cases than had been the case in November and December. Weather conditions probably played some rôle here, but the prevention of transmission of infection from one measles patient to another was undoubtedly of very great importance in securing the low morbidity during February.

Age—The age variation of the patients under treatment was necessarily restricted to the age of soldiers in the army with the exception of a few older men such as officers, cooks and bakers. The youngest patient was 17 years old and the oldest 51. In both lobar pneumonia and bronchopneumonia the largest age frequency was 22 years. The greater number of patients were between 18 and 25 years of age.

Occupation—The majority of the patients gave their occupation as farming. Of 157 farmers with lobar pneumonia twenty-nine, or 18.6 per cent, died. The average total mortality for the disease was 14.9 per cent. Of 265 farmers among the bronchopneumonia patients, ninety-four, or 35.4 per cent, died. The average mortality for this type of pneumonia was 36 per cent. Thus it is apparent that among farmers a fatal outcome was slightly more frequent in lobar pneumonia and equally as frequent in bronchopneumonia as the total respective mortalities. Farmers formed the majority of the latter class. Forty-four different occupations are represented.

ETIOLOGY

Lobar Pneumonia—At the present time we understand two general causes of lobar pneumonia, the first, direct contagion, and the second, infection in individuals whose resistance has been temporarily lowered from exposure to wet or cold or from other causes. Infection with Types I, II or III pneumococci has been shown to result in a high percentage of cases from direct transmission. In the case of infection with Type IV pneumococcus which is found in the bacterial flora of the mouths of 50 to 80 per cent of normal individuals, the possibility of contact infection is more problematic and more remote. The type of pneumococcus in the sputum has been determined by the Avery² method in 139 cases of lobar pneumonia. Ten per cent of these have shown Type I organisms, 7.9 per cent Type II, and the remainder, 82.1 per cent, have been of Group IV. There have been no Type III infections. These results would indicate that the disease as seen in this camp is chiefly a result of exposure among the soldiers to the rigors of outdoor life. The following observations appear to bear out this conclusion.

2 Avery, O. T. Determination of Types of Pneumococcus in Lobar Pneumonia, Jour Am Med Assn, 1918, 70, 17.

A SERIES OF FIFTY PATIENTS QUESTIONED AS TO POSSIBLE FACTORS IN
THE CAUSATION OF THEIR PNEUMONIA

Each of fifty lobar pneumonia patients, admitted for the most part during the month of February, was asked the following series of questions

- 1 Before you were taken sick were you wearing the khaki uniform or olive drab woolen?
- 2 Were you wearing winter or summer underwear?
- 3 How many blankets did you have on your cot? Comforters?
- 4 Were you warm enough at night?
- 5 Was your food satisfactory as to quality? As to quantity?
- 6 How many were sleeping in your tent?
- 7 Was it the regulation pyramidal tent? Otherwise how large was it?
- 8 Did it have a floor?
- 9 Had you a sore throat, cold, cough or "grippe" before you were taken ill this time?
- 10 What illness have you had recently?
- 11 Was anyone else in your tent sick recently? Colds? Cough? Pneumonia?
- 12 Did the men in the tent spit on the floor? On the stove? In the stove?
- 13 Had you recently been out in bad weather? Been on guard duty? Been wet?

The information obtained may be summarized as follows

1 Thirteen, 26 per cent, did not have the woolen blouse All had the wool breeches and winter overcoats.

2 All were supplied with winter underwear

3 and 4 None admitted that bedding was insufficient, claiming to be warm and comfortable at night

5 In practically every instance food was entirely satisfactory

6 The regulation number of men in a pyramidal tent is five In eleven instances there were six men in a tent, three times there were seven, four times there were eight, and only two men reported as many as nine soldiers sleeping in their tent Twenty-two of the patients reported five men in their tent and four had but four men Twenty out of forty-six men were, then, living in more or less crowded circumstances This corresponds to the findings of Surgeon-General Gorgas during the building of the Panama Canal where the incidence of pneumonia fell remarkably when the laborers were removed from barracks into individual cabins

7 All but four slept in the regulation tent

8 Nearly all the tents had floors

9 and 10 Sixty per cent of the patients had had a preceding head cold, 4 per cent had had influenza and 2 per cent were suffering from acute follicular tonsillitis Five cases, or 10 per cent, had had previous measles, but only in one instance did the pneumonia follow it immediately Four per cent had had mumps a short time previously

11 In 32 per cent nobody else in the tent was sick In 26 per cent, both the patient and some of his tentmates were sick In 8 per cent the patient was well but one or more of his mates had a head cold In one instance a tentmate had come down with pneumonia five days previously In connection

with this it is well to refer to the report of Major Zinsser³ from Camp Wheeler, in which he reviews a survey made on certain companies where the type of pneumococcus in the mouth was determined on every individual. He concludes that there is quite definite evidence of infection of tentmates by carriers and that company infection is probably of equal importance to tent infection.

12 Only six instances of promiscuous spitting were reported.

13 Fifty per cent. gave a definite history of exposure and 20 per cent alone had been on guard duty a few days before.

One patient in this series was a hospital orderly who had been in good health and who came down with Type I pneumonia while attending a patient ill with that type of infection.

Bronchopneumonia—Regarding bronchopneumonia it is interesting to note that of 333 patients, fifty-five gave a history of cough, cold or other respiratory tract infection previous to the onset of measles prodromata. Of 333 cases of uncomplicated measles, only fourteen gave a similar history. It would thus appear that preceding upper respiratory tract infection may be a factor in the development of postmeasles pneumonia. On the other hand, the mortality among those cases of bronchopneumonia giving such a previous history was slightly lower than the general bronchopneumonia mortality.

Previous Diseases—It has been suggested by some that the fact that most of the soldiers had been farmers and had not had the usual infections of childhood, accounted in part for the high incidence and mortality from disease in camp, that they had not, through past diseases, had an opportunity to build up some degree of general immunity to infection. The subject of previous occupations has already been discussed. A summary of the incidence of all infectious diseases in the past histories of lobar pneumonia cases gives 561 infections. In other words, there was an average of 2.3 infectious diseases in the past history of each man. Among the bronchopneumonias the histories of infectious disease totalled 497, making 1.4 for each man. Among the bronchopneumonias 47.7 per cent of the ninety patients giving entirely negative past histories died. This is higher than the general mortality of 36 per cent. The mortality among the ten cases of lobar pneumonia with negative histories was 20 per cent as contrasted with a general mortality of 14.9 per cent. These findings would indicate that the foregoing supposition has some basis in fact, but for proof of the contention the results should be compared with results in other camps where the population was chiefly urban.

History of Recent Measles Infection—Of the 333 cases of bronchopneumonia, 292 were secondary to measles, two each followed mumps and otitis media, one case occurred after cerebrospinal menin-

3 Duncan, Louis C. An Epidemic of Measles and Pneumonia in the Thirty-First Division, Camp Wheeler, Ga., Mil Surgeon, 1918, 42, 123.

gitis and fourteen were preceded by influenzoid attacks. In the remaining twenty-two cases no relationship to prior disease was evident from the histories. Only thirty of the total postmeasles bronchopneumonias had been discharged to duty in the interval between the measles and pneumonia.

In the case of lobar pneumonia 148, or over one-half of the patients, had had remote measles infection. Of these, but five cases had been infected during their stay in camp. Cases with recent measles, that is under one month interval, numbered but thirty-one. Of these, six were admitted with the rash and the seventh developed it on the day following admission. The others had been convalescent for one week or longer. We were impressed, first, with the fact that postmeasles pneumonia was, as a rule, bronchopneumonic in type, and second, that whereas bronchopneumonia followed measles with no intervening period of good health, lobar pneumonia, when it did occur, usually following an interval of convalescence.

Incidence of Hookworm—The stools of 159 patients were examined for parasites. Hookworm ova were found in 21.3 per cent. During this same period routine examinations of all admissions to the hospital gave over 20 per cent of positive results. A divisional hookworm survey of 22,898 apparently healthy soldiers showed that 18.6 per cent were found to harbor the parasite. All of these figures correspond quite well. On the other hand, among the bronchopneumonia patients 50 per cent of those who had hookworm died, while only 17 per cent of the negative ones proved fatal. Unfortunately, of the lobar pneumonia patients who died, only two had had hookworm examinations. These were negative. Seventy-three examinations were made on those who recovered, and of these fourteen were positive. Two of the latter passed through a severe illness, two had but a mild pneumonia and the ten remaining had a course of average severity.

History of Alcohol—Among the lobar pneumonia patients alcohol was denied in 136 instances. Moderate use of intoxicants was admitted in eighty-one cases and an excess in seven. Of the members of the first class, 14.7 per cent died, of the second, 17.3 per cent, and in the case of those who drank to excess 14.2 per cent died. All of these mortality percentages correspond well with each other and with the general mortality of 14.9 per cent. In only one instance were there findings which might be interpreted as the results of excessive use of alcohol. Among the bronchopneumonia victims, seventy-nine patients admitted a moderate use of alcohol with a mortality of 41.7 per cent. Of those admitting excess there were eight, of whom two died. It may be stated that alcohol has been of no importance in this camp either in predisposing to pneumonia or in influencing the severity of the disease.

BACTERIOLOGY

Type determination was carried out in the laboratory by the Avery method with the artificial pneumococcus medium as described from this camp by Vaughan⁴. Certain minor modifications have been made during this period. The sputum from each patient was examined routinely on three successive mornings. It is improbable that a Type I, II or III organism would be concealed by a Type IV mouth organism on three successive cultivations. This is borne out by the fact that the organism found in pure culture in each pleural exudate has always been of the same type as that found in the sputum. Moreover, according to the figures of Krumwiede and Valentine⁵ and of Beckler, Marden and Gillette,⁶ who have controlled the Avery method by mouse determination, three cultures would make the results reliable.

The greater number of bronchopneumonia cases occurred during the early months of the camp and at a time when type determination was not being done. The laboratory reports during this period were not comprehensive and have not been included. Among the later cases, the pneumococcus has been found to be the infecting organism in seventy-seven cases. Sixty-four of these cases were typed, and of them fifty-five showed Type IV organism. Nine cases belonged to Type II. In twelve instances streptococci were found as the prevailing organism, and in six additional the pneumococcus and streptococcus were both present. Realizing that hemolytic streptococci had been reported as the cause of bronchopneumonia in several different camps, the laboratory personnel has made repeated attempts to find this organism. They have compared the organisms obtained here with cultures from another camp which has reported nearly universal *Streptococcus hemolyticus* cultures and find that it is not the same organism. The organism causing bronchopneumonia in the majority of cases in this camp is the pneumococcus, usually Type IV.

In lobar pneumonia the types of pneumococci found in 139 cases are distributed 82.1 per cent to Type IV, none to Type III, 7.9 per cent to Type II, and 10 per cent to Type I. As we did not at first have Type III serum the first sixteen Type IV cases should more properly be classed as Type III or IV. Streptococcus was found in one case in association with a Type IV pneumococcus.

4 Vaughan, Warren T. Type Determination of Pneumococcus Infection as Practiced in the Field with Avery's New Cultural Method, Jour Am Med Assn, 1918, **70**, 431.

5 Krumwiede, Charles, Jr., and Valentine, Eugenia. Determination of the Type of Pneumococcus in the Sputum of Lobar Pneumonia, Jour Am Med Assn, 1918, **70**, 513.

6 Beckler, Edith A., Marden, Katherine, and Gillette, Helen H. Pneumococcus Type Determination by Avery's Cultural Method, Jour Am Med Assn, 1918, **70**, 836.

In several instances of pneumococcus culture both for lobar and bronchopneumonia the organisms have grown in short chains which on cursory examination might have been mistaken for streptococci. The diplococcus formation in the chain could, however, be well demonstrated.

Examination for tubercle bacilli has been routine and has been negative in every instance except one case of postmeasles bronchopneumonia. This patient died of a tuberculous bronchopneumonia.

Organisms in Pleural Exudate — Pleural effusion occurred in twenty-four cases of lobar pneumonia that were typed. As a rule, clear fluids containing organisms will go sooner or later to pus formation. In but three cases showing organisms in the pleural exudate was operation not necessary.

CHARACTER OF THE PLEURAL EFFUSION IN TWENTY-FOUR CASES OF LOBAR PNEUMONIA

Character of Chest Fluid	Type of Pneumococcus			
	Type I No Cases	Type II No Cases	Type III No Cases	Type IV No Cases
Pus with organisms	2	1	0	10
Pus without organisms	0	0	0	2
Clear fluid with organisms	0	1	0	3
Clear fluid without organisms	1	1	0	3
Total	<u>3</u>	<u>3</u>	<u>0</u>	<u>18</u>

In regard to bronchopneumonia, the type of organism has been determined in the pleural exudate of eleven cases, in all of which it has been Type IV pneumococcus. *Streptococcus mucosus* has been found in one chest fluid and combined pneumococcus and streptococcus infection in one other. The empyema fluid from every bronchopneumonia typed since March 31 has shown pneumococci, except for two instances with *S. hemolyticus*.

Blood culture determinations have been made in thirty cases of pneumonia and have been sterile in all but three. There have been two positive cultures of Type IV pneumococcus and one of Type I.

LOBAR PNEUMONIA—SYMPTOMATOLOGY

As the first few cases were being treated and studied we were under the impression that the disease was not the classic pneumonia with sudden onset, chills, fever, pain, cough, rusty sputum and crisis. The following observations are convincing evidence that the pneumonia here treated is the same real pneumococcus lobar pneumonia with which all are familiar.

Character of Sputum — In eighty-two the sputum was described, and of these, 81.8 per cent had rusty sputum, 1.2 per cent, prune juice, 6.1 per cent, thick and tenacious, but not bloody, and 10.9 per cent, mucopurulent.

History of Chill—In 50·8 per cent of the 234 cases there was a history of sudden onset and chill. In 23·1 per cent the history indicates that there was no chill. In the remaining 26·1 per cent the information is indefinite. At least one-half and possibly as high as two-thirds of the patients, then, had a chill at onset.

Pain and Friction Rub—Very nearly all complained of pain in the side. In five cases the pain was on the opposite side from that in which consolidation had occurred. Although the pain was pleural in character a friction rub was found in but 19·7 per cent of the cases.

Character of Fever—One hundred and ten patients ran a high fever with a mortality of 14·5 per cent. Of the sixty-five with a moderately high fever, 13·9 per cent died. Thirteen had a moderate elevation of temperature, with no deaths. Of the eight who ran a low temperature, usually below 101° F., 37·5 per cent died. The highest mortality is recorded in those running a low fever. The small number of patients in this class detracts from the value of the high figures, but these findings do correspond to the common statement that pneumonia patients with high temperatures and vigorous reaction to infection frequently do better than those running low temperatures. Of the three men who died after running a low fever, the first had had a moderate alcoholic history and developed a measles rash on the day of admission. No other complications occurred. The second had a consolidation of the entire right lung. The third was a casual admission from a passing troop train, had been sick six days before admission and was suffering from a consolidation of the entire left lung together with a left serofibrinous pleurisy.

Two-fifths of the patients had a typical crisis. Pseudocrisis was noted in eight instances. Two cases had a critical fall on the second day and one on the twelfth day. There were instances of crisis on every day intervening between these two extremes. The greatest number, however, was on the seventh day, being twenty-five, as contrasted with fifteen on the sixth and twelve on the eighth. As contrasted to eighty-eight instances of crises there were seventy-eight of lysis and in the remainder, the character of temperature fall could not be determined because of the incidence of complication or of death.

Lobes Involved—As usual, the right lower lobe was consolidated most frequently. The other lobes in order of frequency were left lower, right upper, right middle and left upper. This is the usual order of frequency as may be seen by a comparison with the figures of Cross⁷ covering 340 cases in the Minneapolis City Hospital. His order differs only in the fact that the left upper was involved more

⁷ Cross, J. G. Analysis of Two Hundred Cases of Lobar Pneumonia, Jour. Am. Med. Assn., 1915, 65, 1778.

frequently than the right middle. In our series there were one hundred instances of right-sided involvement, ninety-six of left involvement and nine of bilateral consolidation. In the five remaining, which were cases treated in the early days of the hospital, the lobe affected was not noted. The records show that the mortality increased regularly with increase in the number of lobes involved. In the two patients who had consolidation of four lobes 100 per cent died.

Other Symptoms—*Abdominal tenderness* of marked degree without abdominal complications occurred three times and the possibility of appendicitis was suspected in two additional patients. These were not operated on. *Nausea* was one of the early symptoms in eight instances and vomiting occurred in sixteen, of whom 19 per cent died. *Abdominal distention* may be considered as of bad prognosis. Of nineteen cases with distention, approximately 50 per cent died. *Icterus* occurred in nine instances. The mortality among those showing this symptom was 44 per cent. Severe *cyanosis* occurred in twenty-nine cases and delirium in twenty-one. Of the former, 45 per cent died, of the latter, 33.3 per cent. Five cases were described as drowsy and all recovered. *Heipés* were noted on the lips seventeen times. Meningitis was suspected in four cases on which lumbar puncture was performed. There was no increase in the spinal fluid cell count and the patients subsequently ran typical courses of pneumonia. In all four cases the consolidation was right-sided and the right upper lobe was involved in three out of the four cases. The illness was severe in three of the patients, but only one died.

Duration—The average duration of the stay in the hospital computed for 152 consecutive patients was thirty-three days.

BRONCHOPNEUMONIA

As has previously been stated, bronchopneumonia developed in the majority of instances after measles. There was usually no intervening period of good health, the ordinary postmeasles bronchitis became more severe, the temperature did not drop and the chest signs became more numerous. In thirty cases there was an interval of comparative good health and the patients had gone back to duty, but a careful questioning developed the fact that they were never well or entirely free from respiratory troubles during the interval. In two instances the pneumonia came on as long as thirty-three and thirty-five days after the patient had been discharged for measles.

Onset—The onset of the pneumonic process was usually gradual. In only twenty-four cases was it sudden and in eighteen of these the differential diagnosis from lobar pneumonia was very difficult. Thirty patients, or 9 per cent, reported a chill at the beginning of their illness.

This chill was never severe and never seemed comparable in degree to that accompanying lobar pneumonia

Character of Sputum—The sputum was reported as being rusty in but three cases of this entire group. In these three cases the signs were those of bronchopneumonia and not of lobar pneumonia. Sputum was recorded as bloody in a few instances, and as greenish purulent in three. The vast majority of patients had mucopurulent sputum which was raised without great difficulty

Cough and Hoarseness—Cough was the most frequent single symptom. It was usually distressing, long continued and often provoked by motion, eating and drinking. In some cases it was markedly productive, while in others it was very scanty in its results. Hoarseness was recorded in one hundred and seventeen instances and 50 per cent of patients in this group died. The symptom came early and lasted long after the patient was up and about the ward. In a few instances the hoarseness lasted for months. One such case is of interest, in that in view of the persistent hoarseness a Wassermann reaction was made and found to be strongly positive. The hoarseness had not been present before the onset of the bronchopneumonia. In these cases no lesion in the vocal cords, other than that of acute inflammation, was demonstrable

Pain and Friction Rub—Pain was not as frequent nor as persistent as was the case in lobar pneumonia. A friction rub was described in thirty-nine cases, and in these there was usually some associated pain

Character of Fever—In 265 patients the fever was either remittent or intermittent in type. Twenty-six cases had a continued type fever at some time during the course of the disease, but never throughout its entire extent. Many showed wide diurnal sweeps of temperature. This was especially true in the empyema cases. In 274 cases the temperature ranged during the height of the disease between 102 and 104 F. There was a single temperature record of 106 and a few over 105. The average duration of the fever for all the patients was fourteen days. Two uncomplicated cases had recurrent temperature for sixty days. At times the highest temperature record of the day was registered during the morning hours

In but one case of pneumonia, diagnosed bronchopneumonia, was there a temperature fall by crisis. This patient had signs unmistakably against lobar pneumonia. In thirteen additional instances there was a critical fall of temperature, but it subsequently rose and continued irregular. In all of the remaining cases defervescence occurred by lysis over a more or less protracted period of time. Relapses were frequent

Respiratory Rate—In bronchopneumonia as well as in lobar pneumonia study of the pulse rate did not result in noteworthy findings. The important fact as regarding respirations was the low rate as compared with the lobar pneumonia. The majority of the patients had a respiratory rate around twenty-five per minute. Two hundred and forty-six men fell into this group. Respirations in bronchopneumonia, as well as in lobar pneumonia, have been recorded as high as sixty per minute before a fatal termination.

Physical Findings—One of the characteristics of the physical findings in the bronchopneumonia patients at this camp has been their inconstancy and polymorphism. One-third of the series had bilateral râles which, at one time or another, were of nearly every description. Usually the coarse, moist râles of bronchial origin are transmitted to nearly all parts of the chest while the fine showers of pneumonic crepitation are limited to isolated patches. Signs of consolidation were fleeting and of uncertain size. In one-tenth of the cases bilateral râles of variable description furnished the only signs of pathology in the chest and in this series 33 per cent died, a mortality practically identical with the general mortality. In two hundred and ten cases there were bilateral signs of consolidation. In some the signs were chiefly unilateral. One of the most frequent sites for consolidation lies to the vertebral side of either scapula. Consolidation is also frequently reported as being at the angle of the scapula.

Other Symptoms—*Cyanosis* of marked degree was very frequently observed, especially in those desperately ill. Forty out of fifty-three severely cyanotic cases proved fatal. *Sweating* was frequently observed. The easily raised mucopurulent sputum, together with cyanosis and sweating, furnish a picture quite distinct from that seen on lobar pneumonia. *Hei pes* was noted seven times, *jaundice* five times and *epistaxis* ten times. Nineteen patients were *delirious*, of whom eleven died. As a rule, one of the characteristics seen in our bronchopneumonia patients was a clear mental condition up until the time of death. *Distention* appeared in nine cases, of whom 44 per cent died. The respiratory grunt characteristic of lobar pneumonia was never noted.

Course—In regard to the course of the disease, there are three well-defined groups of cases. In the first group are those severely ill patients who at a very early period show signs of extensive and severe pulmonary damage and who die promptly, or more rarely, show early signs of improvement and finally recover. Fifty per cent of our patients who were fatally ill died within ten days from the onset of their disease, while 75 per cent died within less than fifteen days. The second type consisted of a protracted illness over a long period.

of time and usually resulted in recovery. In this class complications were chiefly responsible for the long duration of stay in hospital. Comparatively few complications figured in the first group of cases. In the third class of cases were persons who had been moderately ill and who seemed to be convalescing favorably, but who experienced either one or many relapses. Some recovered and many did not. There were not necessarily complications in this class, although they frequently did occur. At times, there were few pulmonary signs to account for the relapse or for its severity. The presence of pus in the pleural cavity was frequently suspected and the record of unsuccessful needlings is evidence that this was not the cause.

Duration—The average duration of stay in hospital for the 333 cases was between thirty-four and thirty-five days, a period surprisingly similar to that for lobar pneumonia.

DIFFERENTIAL DIAGNOSIS

It is natural that with so many cases of lobar and of bronchopneumonia, and with all grades of both conditions, it was at times extremely difficult to determine which disease was present. Physical signs may be atypical and unconvincing. The history may give no definite clue as to the condition. Certain rules, each having its exceptions, have aided in the diagnosing of these borderline cases. The *character of the sputum* was one of the most helpful aids. If it is thick, tenacious and especially blood-streaked or rusty, the involvement is presumably lobar. Of the cases of lobar pneumonia, 82 per cent showed rusty sputum, whereas among bronchopneumonias, less than 1 per cent of sputums were described as rusty. In this camp we found that with a history of *recent measles* infection and without an intervening period of fair health, the probability is that the condition is one of bronchopneumonia. *History of chill* with sudden onset is still characteristic of lobar pneumonia, being present in over 50 per cent of cases, as contrasted with 9 per cent in bronchopneumonia. The *fever* in lobar pneumonia is usually high and is more apt to be continued in character. In bronchopneumonia it tends to run lower and is frequently remittent in character, falling at times as low as 99 F, or even to normal. In the latter condition the diurnal variation is apt to be greater. Among the physical signs the presence of widely distributed, bilateral, medium and coarse, *moist râles*, and patchy distribution of constant sized crepitations of alveolar involvement are more definitely characteristic of bronchopneumonia than are the presence and distribution of definite signs of consolidation. We wish to emphasize the finding of Cole⁸ who, in speaking of bronchopneumonia, states

⁸ Cole, Rufus, and McCallum, W. G. Jour. Am. Med. Assn., 1918, **70**, 1146

In no uncomplicated cases have we seen wide areas of dulness with characteristic tubular breathing and other signs of consolidation. When these signs have been present there was always a complicating lobar pneumonia. In a few cases, however, later in the disease there has been impairment of the percussion note over a wide area, with quite distant tubular breathing over this area, but with voice sounds fairly well transmitted. The repeated insertion of a needle in these cases has failed to reveal fluid and the needle has felt as though it were in a more or less solid lung. We have interpreted these signs as due to a wide-spread involvement of the lung with a marked degree of proliferation and plugging of the bronchi.

We subscribe to the foregoing statement, but record one important exception. In our experience a patient with bronchopneumonia may have signs of consolidation over one entire base and not have lobar pneumonia. As was proved at necropsy in one such case, there was a massive empyema of that side with a completely collapsed lung, which was bound down to the posterior chest wall with pleuritic adhesions. In this particular instance sounds were also fairly well transmitted over the fluid. One further point noted by Cole is that there may be a combined infection and both types of pneumonia may be present in the same individual. Rarely the diagnosis may "hang fire" for many days, in which case the presence or absence of a temperature fall by crisis will aid in a decision.

COMPLICATIONS

Empyema—This condition has been found as early as the second day of the disease. Here it is a question as to whether the empyema is not a primary condition, a question whether or not there is pulmonary consolidation behind the fluid accumulation. Two or three cases were admitted as pneumonia with a history of sudden onset with chills, fever and a pain in the side a short time previous to admission, and a history of measles a few weeks previously, who on physical examination showed, not the signs of pneumonia but those of fluid. Their general appearance and behavior also resembled pneumonia, but the presence of sweating suggested again purulent pleurisy. Thoracentesis on these cases bore out the diagnosis of empyema. There was no convincing evidence of accompanying pulmonary consolidation. Such cases seem to be the end-stages of a measles sequence. It is possible either that an unrecognized serofibrinous pleurisy was present from the time the patient was discharged after his measles, which had just become purulent, or that, as the result of the extensive damage done to the respiratory tract by the measles virus, there had occurred a primary empyema. The pneumococcus was found in the fluid.

Empyema may be present with a normal temperature. One patient who was entirely convalescent from his pneumonia and who had had a normal temperature for fourteen days was found, on the examina-

tion preliminary to discharge, to have one side of his chest entirely flat to percussion. Aspiration showed pus and at operation several pints of the material were drained.

Signs of fluid may be equivocal, but we have usually found them to be decidedly more definite in our cases of lobar pneumonia than in our bronchopneumonias. Flatness to percussion has been one of the two most reliable signs. With it there may be distant sounds or the bronchial voice sounds may be transmitted fairly distinctly. The breath sounds are less often transmitted through fluid than are the voice sounds. We have found cases of serofibrinous pleurisy with flatness, diminished tactile fremitus, absent breath sounds and distinctly transmitted bronchial whispered voice or egophony, in which the fluid was not purulent and there was no consolidation. The bronchial voice sounds presumably originated from a totally collapsed lobe. Flatness to percussion is not always present over fluid, especially so in the case of bronchopneumonia. Of equal importance to flatness on percussion is absence of or a very faint transmission of breath sounds even though there be but moderate dulness. This absence of complete flatness may be accounted for, perhaps, by presence of a fringe of lung tissue overlapping the fluid and tending to come between that and the chest wall. In favor of this supposition is the fact that very frequently it is necessary to insert the needle to a distance of $1\frac{1}{2}$ inches or more before fluid can be reached. Opposed to this is the fact that no condition just like that described has been found at necropsy with the exception of some cases of interlobar empyema and of encapsulated pus in the pleural cavity adjacent to the mediastinum. Râles, usually coarse and sticky, may be present over an area containing fluid. It is never safe to say that because râles are present and seem close to the ear, fluid is absent. It is rare, however, to hear typical showers of fine, pneumonic crepitations over fluid.

The positions of the cardiac borders, apex impulse and point of maximum intensity of the heart sounds are of great importance. Diminished respiratory excursion on one side is most suggestive of fluid accumulation in considerable amount on that side. The patient's general condition is of aid in arousing the suspicion of fluid, but does not enable one to make the diagnosis. The typical septic appearance, the flushed cheeks, the moist skin, a slightly icteric tinge to the skin and the presence of sweating, especially at night, are the points of importance. In lobar pneumonia the presence of sweating had been of material benefit. In bronchopneumonia this feature is frequently present without empyema and due presumably to the purulent bronchitis.

Determination of the presence or absence of Grocco's paravertebral triangle has not given great assistance. The roentgen ray has been

helpful in some cases, but it has not increased materially the number of instances in which fluid has been found. In but one class of cases has the roentgen ray been indispensable, namely, interlobar empyema and allied conditions.

In this camp, as at other camps, collections of pus have been found at necropsy substernal, in the mediastinum, and in the pleural cavity between the lungs and the pericardium or mediastinum. The roentgen ray has enabled us to find these encapsulated fluids in time to treat them. For example, one patient was tapped early in his illness and 15 c c of a serofibrino-purulent fluid containing pneumococci was withdrawn. The fluid was not found until the needle was inserted to its full length. Several subsequent thoracenteses were nonproductive. Later, after the acute condition had subsided and the temperature was running from normal in the morning to 99 or 101 F in the afternoon, the roentgen ray showed a shadow between the mesial surface of the right lower lobe and the pericardium. A needle was then inserted deep into the eighth right interspace, 8 cm from the spinous processes, and thick, creamy pus was withdrawn. Thoracotomy was done and the patient is now about ready for discharge. We have another patient in the ward at present, convalescent from bronchopneumonia, who has the classic signs and symptoms of an abscess in the mediastinum with substernal pain, increase in retrosternal dullness, a mediastinal shadow shown by the roentgen ray, unequal pupils and pulses, and the constitutional signs of pus.

Too great emphasis cannot be placed on the statement that if one is convinced from the signs and general condition that fluid is present, needling should be persisted in even though no fluid be at first obtained. One example will suffice.

A patient who had lobar pneumonia was suspected of having fluid extending from the region of the cardiac apex around to the region of the left scapular angle. A needle was inserted in this latter area and no fluid was obtained. It was then inserted in the fourth intercostal space anteriorly, about 5 cm outside of the nipple. No fluid was obtained. It was immediately reinserted one interspace lower, not 1 inch from the previous point, and a purulent fluid was withdrawn. Two hours later, at operation, over a pint of pus was drained from this region.

Another maneuver in the successful demonstration of fluid is in directing the needle in more than one direction after it has once been inserted. One more point to be borne in mind is that, before tapping the patient should be so placed that the suspected area is as nearly as possible the dependent area.

Encapsulated fluid has seemed to be the rule rather than the exception. The cases described in the foregoing serve as examples. In truth, there is scarcely an area in the chest surface, with the exception

of the precordium and the apices, from which we have not been able in one case or another to obtain fluid. In one case of lobar pneumonia in which we were convinced that pus was present we obtained it only through the region of the right nipple. At operation the surgeons preferred to perform a posterior rib resection. No pus was obtained and it did not appear until a secondary operation was performed when the adhesions were well broken up. Occasionally, encapsulated fluid will occur in two separated areas in the same chest.

Patients who had bilateral empyema, of which we have had seven, have not recovered.

We have generally been able to find fluid before it has become purulent and have been able by repetition of needling to determine the most desirable time for operation. This optimal time is a question on which there is still considerable difference of opinion. Some cases of serofibrinous pleurisy have been sent to the surgeons as soon as the fluid has been proved to contain organisms. The reason for this early transfer was the argument that the condition, provided organisms were present in the fluid, was somewhat analogous to that of an acute appendicitis in which one would invariably operate by preference long before the development of frank pus. In other cases we have waited until the fluid has become purulent. Out of twenty-one patients in whom the fluid at operation was of the former type, eleven died. Out of nineteen in whom it was described as definitely purulent, but two have died. We feel that the best procedure is to tide the patient through the acute pneumonia by complete aspiration as long as the fluid is relatively clear, and after that to continue aspirations if the patient is improving, otherwise to operate. In some instances the critical condition requires an early operation. This is especially true in bronchopneumonia, in which condition the fluid may never become pus, the patient dying before that time. Operation has, therefore, been done earlier on such critical cases and sometimes has without doubt been a life-saving procedure. Rib resection has been the operation of choice, although in some of the severely ill a thoracotomy has been done. The results with our patients who were operated on for empyema have been fairly satisfactory, the mortality being about 28 per cent.

There are two periods during the course of acute lobar pneumonia at which the signs may very strongly suggest a pleural effusion which is, in reality, not present. The first is early in the disease when the signs of consolidation have not developed fully and when there may be dulness but usually not real flatness, with suppression of the breath and voice sounds. If the beginning consolidation is in the lower lobe, fluid may be strongly suspected. In fifteen of our cases these signs were present. The second and more important period is

at or about the time of crisis and resolution. Following the presence of dulness, bronchial breathing and bronchophony, there may develop distant bronchophony and dulness to flatness over the same area. Thoracentesis will be nonproductive and on the same day or soon thereafter, the temperature will suddenly drop to normal where it will remain. We know of no accepted anatomic explanation for this phenomenon, but suggest that with beginning resolution more air enters the central portion of the lobe, in the region of the larger bronchi, and consequently the bronchial breathing and bronchophony become less distinct. The still considerable amount of consolidation accounts for the persisting dulness. As the resolution progresses this dulness also clears up. We have had twelve such cases in which fluid was suspected and some of which were tapped with negative results.

One notable difference between the bronchopneumonias of this camp and of certain other camps is in the comparatively lower incidence of empyema. There have been until March 31, but twenty-nine cases of post-bronchopneumonia empyema. Of twenty-six necropsies on bronchopneumonia patients, but ten had empyema. Nearly all of these were postoperative cases. In the ninety-four earliest cases of bronchopneumonia in which the patient died no necropsy was made. These may have had a high proportion of empyema. But among the two hundred and thirty-nine who either recovered or were examined at necropsy, the incidence of empyema was 8.2 per cent. The true percentage was not lower than this figure and presumably was several points higher on account of possible empyema in the ninety-four cases in which no necropsy was made. We cannot give definite figures as to the percentage of empyemas following bronchopneumonia, but draw attention to the fact that the apparent relative infrequency of empyema corresponds well to the fact that the pneumococcus, rather than the hemolytic streptococcus, was the infecting organism. The empyema percentage in lobar pneumonia was 13.5.

Pericarditis — This complication occurred in nine cases in the series. There have been three additional instances in more recent cases. It is of bad prognosis. Of these twelve patients, nine died, one is still seriously ill and the other two, after a stormy illness, recovered. In the majority of instances pericarditis is a terminal complication.

Urticaria — This condition has occurred as a part of serum sickness in cases treated with Type I antipneumococcus serum. It has also occurred in two instances of the lobar pneumonia series and in three additional cases since March 31, when no serum has been given and no cause could be found. In these latter cases the rash usually came out around the time of crisis, and we suggest that it may be an evidence of sensitization reaction, either to the proteins of the pneumo-

coccus or to some protein derived from the exudate itself Allied to this is another case diagnosed as idiopathic purpura in which there developed cutaneous manifestations, similar in character to erythema multiforme There was an accompanying spontaneous bleeding from the bowels No cause was discovered Rectal examination was negative, except for some tenderness high up The patient had two attacks at short intervals and was discharged in good health

Peritonitis—As a complication of lobar pneumonia we have had, in the series quoted, one case of peritonitis as shown at necropsy, and, since March 31, we have had three additional cases The first, at necropsy, had not only a purulent peritoneal exudate, but also pus in both pleural cavities and in the pericardium, a condition which we choose to designate for lack of a better term, as suppurative polyserositis One or two other patients have been in the wards in whom peritonitis had been very strongly suspected The patients died, but necropsy could not be performed

Two of the peritonitis cases are of interest as being postoperative The first of these was operated on for appendicitis and developed a postoperative pneumonia which was, in turn, followed by general peritonitis and death At necropsy the consolidation was found to be in the stage of resolution The interesting feature was that a culture of the peritoneal exudate showed the infection to be pneumococcic In the second case, several days after an appendix operation, lobar pneumonia developed, which was followed by a pneumococcus empyema, a general peritonitis and death The appendix scar had nearly healed over Here again pneumococci were found to be the invading organism of the peritoneum

The symptoms of peritonitis, complicating pneumonia, are usually quite indefinite There is more or less abdominal distention and some tenderness on pressure Muscle spasm may be slight or absent The pathologic picture is one of a thin layer of yellow greenish pus covering various portions of the intestines and found particularly between coils and down in the folds There is very little accumulation of peritoneal fluid

Arthritis—Following lobar pneumonia the acute suppurative form of synovitis, as well as cases with the classic symptoms and signs of acute rheumatic fever, have been noted Pneumococci were isolated from the joint of two of these cases with suppurative synovitis Salicylate did not appear to have great effect on the "rheumatic fever" type of case

Other Complications—There have been several cases which have developed *multiple complications*, so that the patients have had to remain in the hospital for months One patient, after a pneumonia of the right lower lobe, developed a right empyema, a fibrino-purulent

pericarditis, an empyema of the left pleural cavity and finally died. At necropsy there was found, in addition to all of this, a purulent mediastinitis. Another patient who had been convalescent for seventeen days from lobar pneumonia, involving the left lower lobe, developed a bronchopneumonia with a right-sided empyema and died. Pneumococci, Type IV, were found in the pleural exudate. Another sequence reported is of measles, bronchopneumonia, purulent otitis media, empyema, terminal lobar pneumonia of the opposite side and death. Yet another individual, admitted with a postmeasles otitis media, later developed a mastoiditis which was operated on. Then followed a post anesthetic lobar pneumonia, a right serofibrinous pleurisy without organisms, an acute purulent synovitis of the right shoulder joint and finally mumps. This patient was also a hookworm host and this may have accounted in part for the numerous complications. He was later discharged well.

Among others of the more important complications of both forms of pneumonia, may be mentioned serofibrinous pleurisy, otitis media, mastoiditis, laryngitis, an anaphylactic reaction to intravenous serum in four cases, and metastatic interstitial abscesses. Otitis media and mastoiditis deserve further mention. They were of rather high incidence during December and early January, but in the latter half of our series these complications have been decidedly less frequent. Among the lobar pneumonia patients right otitis media occurred ten times, left involvement six times and bilateral involvement in five instances. Five cases progressed to mastoid involvement. Among the bronchopneumonia patients there were fifty-eight cases of otitis media, with twenty-four in the right, twenty on the left and fourteen bilateral. Seventeen cases of mastoiditis resulted therefrom.

PNEUMOCOCCOSIS AT CAMP SEVIER

Not only has the laboratory force been unable to demonstrate the presence of the hemolytic streptococcus in the cases of bronchopneumonia, but also they have found that the pneumococcus at this camp might aptly be termed omnipresent. We have had five cases of pneumococcus meningitis, not secondary to other disease. One of these was due to Type I pneumococcus. We have had cases of primary otitis media and mastoiditis in which the pneumococcus was found in pure culture. There is one patient in the hospital suffering from a spondylitis and a psoas abscess. Type I pneumococcus was found in pure culture in the pus. There are two patients with a Type I pneumococcus infection in the form of a chronic bronchitis. The organism in both of these cases has been obtained directly by lung puncture. During a meningitis survey of several companies of the division, the pathologists have frequently found nearly pure cultures of pneumococcus in the nasopharynx. Many other instances might be included.

SPECIFIC TREATMENT

In view of the good results reported from treatment of Type I pneumonia with Type I immune serum we have grouped all cases of pneumonia admitted since the middle of December, 1917. Type determination with the use of the mouse is, admittedly, the more accurate method and should be employed wherever practicable. In the absence of mice we have used Avery's cultural method with satisfactory results. Emphasis should be placed on the desirability of making repeated sputum cultures on the same patient. Every report of Type IV pneumococcus is a negative report. It means that, other than the presence of the diplococcus, nothing definite was found. We have insisted on at least three type determinations on every patient. Perhaps the greatest disadvantage in the method is in the fact that occasionally a Type IV report is followed the next day by one of Type I on the same patient and a day is thus lost for serum treatment. We have taken the three specimens on three successive days. We recommend that it would be much better to take them all on the first or first and second days. Careful collection of real sputum and careful washing thereof will eliminate nearly all of this trouble.

In the treatment of Type I cases with homologous serum, desensitization and intravenous administration were carried out according to the technic outlined by Avery, Chickering, Cole and Dochez.⁹ We found certain precautions to be essential: (1) The first 15 cc should be given very slowly, taking in all about fifteen minutes. If this procedure is followed there is very little danger, even with sensitive patients, (2) watch the respirations, and if they become accelerated, discontinue administration until it can be determined whether this is a beginning anaphylactic reaction, and (3) watch for evidences of peripheral irritation and for urticaria.

In from five to ten or more minutes after serum has been given intravenously to a sensitized individual, he will evidence slight uneasiness. He may rub his heels on the sheet or his legs against each other. He may scratch various portions of his body while complaining of the tingling. Or his first symptoms may be respiratory. His breathing will gradually increase in rapidity. If the nurse has her elbow over the patient's chest or abdomen he may push it aside, complaining of the weight or that it interferes with breathing. The respirations increase until the breathing is rapid, deep and labored as when one has just finished a hard run. It is not the shallow panting of an hysterical individual, nor has it exactly the typical wheezing expira-

⁹ Avery, Chickering, Cole and Dochez. Acute Lobar Pneumonia, Monographs of the Rockefeller Institute for Medical Research, No. 7.

tions of the asthmatic. The impression is given of a great increase in pulmonary ventilation. Respirations may become so labored that the patient cannot reply to questions. He is alert and apprehensive. As the dyspnea becomes very marked moderate cyanosis develops. By this time urticaria is usually quite widespread. If in the region of the eyes they may swell nearly shut. This anaphylactic reaction is combated by immediate discontinuance of serum administration and the intramuscular injection of atropin and epinephrin. The patient rapidly improves and in fifteen minutes from the height of the reaction appears none the worse for the experience. It is advisable not to give additional serum within less than one hour's time.

Type I pneumonia, as has been previously noted, has been rather infrequent in this camp. Ten per cent of the lobar pneumonias were infected with this organism, while none of the bronchopneumonias were so infected. Ten cases have been serum treated. Four cases treated early in the disease had a temperature fall to around normal within twenty-four to thirty-six hours and with immediate amelioration of symptoms. They did not suffer any relapse. One patient with consolidation of the right upper lobe had a crisis with a normal temperature on the third day. That evening a temperature of 104 F developed, and the inflammation spread to the right lower lobe. Two serum administrations brought the temperature to below 100.5 F, from which it did not again rise.

In the case of one patient 90 c c of serum were given on the sixth day. At the end of twelve hours the patient had passed through the crisis. Convalescence was uninterrupted. One further case, first treated on the fifth day, was given two 100 c c doses and the temperature reached normal within twelve hours from the last administration. A subsequent serous effusion, without organisms, appeared and disappeared without requiring special treatment. One case who had previously developed fluid with organisms in his chest improved markedly under serum treatment, but did not recover completely and rib resection was subsequently done for the empyema. He recovered. He had been extremely ill and serum undoubtedly was the means of saving his life.

Two of our serum treated patients died. The first case did not receive serum until at a time when he was moribund and after he had developed a massive empyema. The other patient had received a sufficient amount of serum, 500 c c in all, but did not respond to treatment and died without any recognizable complications having occurred. Treatment in this case was also instituted rather late. A necropsy unfortunately could not be obtained.

Type I immune serum is a most valuable addition in the treatment of pneumonia. It should be used in all cases of Type I infection, the

earlier in the course of the disease the more satisfactory will be the results

Polyvalent serum was used in a few cases of severely ill bronchopneumonias and without beneficial results

MORTALITY

In lobar pneumonia the mortality for the entire period from the opening of the hospital until March 31, 1918, was 14.9 per cent. Our highest number of deaths occurred during the early days of the hospital. In a period from December 1, 1917, until March 31, 1918, during which more accurate records were kept, type determination was made, better methods of isolation were employed and the treatment was supervised in all wards by one individual, the mortality was decidedly lower, being 10 per cent. In this second period nearly all of the cases fall, 201 out of 234. Ten per cent should, then, be more properly the average death rate from the disease in this camp. Among those earlier cases in which the patient died, the records at times leave some doubt as to the possibility of the death being due to an intercurrent, or a primary empyema, rather than to lobar pneumonia.

The death rate with Type I pneumonia is recorded as 14 per cent, and from Type IV as 7 per cent. There were no deaths among the eleven cases of Type II pneumonia. The Type I mortality includes both serum treated cases and those not so treated.

In bronchopneumonia the death rate has been 36 per cent.

CONCLUSIONS

It is a generally recognized fact that statistical reviews are subject to erroneous interpretation and may lead to false conclusions. Yet without such compilations in the past, the progress of medical knowledge would have been considerably retarded. We have felt that a study made by the persons who have had in charge the care and treatment of the cases and who have been led into definite points of view from personal contact with the patients, will be of greater value than a compilation of statistics from various observers in numerous camps. The authors have therefore undertaken to present their experiences and conclusions regarding pneumonia and empyema at Camp Sevier and to verify these findings with the use of figures. From our observations we are led to conclude that the pneumonias as seen in this camp do not comprise an hitherto unknown form of disease, but are in essentials, the same clinical types of the diseases as have been previously described.

THE TREATMENT OF BRONCHIAL ASTHMA WITH PROTEINS¹

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In a recent paper¹ many important clinical facts were brought to light from the study of a series of 400 patients with bronchial asthma. These facts all have a direct bearing on the determination of the cause of the condition and therefore indirectly they indicate the proper treatment. Among other facts, it was shown that 48 per cent of the 400 patients were sensitive to some type of protein and that the younger the patient was when he began to have bronchial asthma the more apt was he to be sensitive to some protein. A table was presented showing the number of patients who were sensitive to the four chief sources of protein, namely, animal hair, food, bacteria and pollens, at the various ages of onset of bronchial asthma. The skin or cutaneous test was employed to determine whether or not the patients were sensitive.

The object of the present paper is to give the results of the treatment of sensitive patients with the proteins to which they were sensitive. Incidentally the relative importance of positive skin tests with various proteins in the same patient will be shown. Only those patients who were sensitive to the proteins in animal hair and in food will be included in this paper. The method of performing the skin test has been frequently described so that it will be omitted here, however, it should be said that in this paper a reaction to be called positive must present an urticarial wheal measuring at least 0.5 cm in diameter. Therefore, as regards the proteins of animal hair and foods, these must give a definite reaction in order to be called positive, smaller reactions should be noted and repeated and frequently they give valuable information, but in this paper, to be conservative, small reactions are ignored. The method of treatment of the sensitive patients will not be given in detail since this has been described in previous papers.²

In the series of 400 patients, 67 were sensitive to the proteins of

¹ Submitted for publication July 30, 1918.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1 Walker, I. C. A Clinical Study of 400 Patients with Bronchial Asthma, *Boston Med and Surg Jour*, 1918, **179**, 288.

2 Walker, I. C. The Treatment of Patients with Bronchial Asthma with the Proteins to which They Are Sensitive, *Jour Med Research*, 1917, **36**, 423.

Other papers on the study of bronchial asthma made possible through a gift by Mr. Charles F. Choate, Jr., of Boston, to the Peter Bent Brigham Hospital are as follows: Studies I-V, *Jour Med Research*, 1917, **35**, 373, 391, 487, 497, 509; Studies VI-VIII, *Jour Immunol*, 1917, **2**, 227, 237, 243; Study IX, *Am Jour Bot*, July, 1917; Studies X-XIII, *Jour Med Research*, 1917, **36**, 231, 237, 243, 295; Study XIV, *ibid*, **36**, 423; Study XV, *ibid*, 1917, **37**, 51; Studies XVI and XVII, *ibid*, 1917, **37**, 277, 287; Study XVIII, *Jour Am Med*

horse dandruff, that is, 17 per cent of the whole series and 35 per cent of the total sensitive cases were sensitive to horse dandruff. Of the 67 patients, 48 were treated with desensitizing doses of horse dandruff proteins with the following results: 30 patients were relieved of asthma, 8 were not improved at all, 5 have been treated too short a time to warrant a definite prognosis, and in the remaining 5 cases it is difficult to state how much the improvement was really due to horse dandruff treatment, because other treatment was given at the same time. Therefore, of the total patients who were both sensitive to and treated with horse dandruff proteins, in 63 per cent there was relief from asthma, in 20 per cent, because of other or of insufficient treatment, it is impossible to state the results of horse dandruff treatment, although in these cases such treatment cannot be considered a failure, but in the remaining 17 per cent horse dandruff treatment was a failure as regards the relief of asthmatic attacks, and therefore only in this 17 per cent, or 8 cases, one might conclude that the skin test was misleading. Five of these patients, however, were sensitive to, and were relieved by, the omission of wheat, and in these 5 patients there was no indication for treatment with horse dandruff, since the positive skin tests with wheat explained the cause of asthma, horse dandruff treatment was given only to see whether or not it would desensitize against wheat, and it did not, thus showing a specificity in the protein treatment. Therefore, in only 3 cases did positive skin tests fail to explain the cause of asthma.

In a previous paper¹ the importance of the age of onset and the duration of asthma was emphasized, therefore, it might be well briefly to summarize these facts as concerns those patients who were relieved by treatment with horse dandruff proteins.

In 8 patients attacks of asthma began at approximately 1 year of age and the duration, at the time treatment was begun, varied between six and thirteen years, 2 patients had had asthma for 13 years, 3 for 11 years, the other 3 for 6, 7, and 9 years, respectively. In 5 cases, asthma began at approximately 2 years of age and the duration at the time of beginning treatment was from 8 to 28 years, the actual duration in each case was, respectively, 28, 25, 12, 10, and 8 years. In 7 patients the onset of asthma was between the ages of 3 and 5 and the duration up to beginning of treatment was from 6 to 31 years, or respectively, 31, 16, 15, 10, 7, 6, and 6 years. In the remaining patients the age of onset was at 9, 10, 12, 22, 23, 26, 40, and 43 years of age and the duration was, respectively, 20, 23, 32, 1, 25, 5, and 2 years. Therefore, of the 30 patients who were sensitive to and relieved by horse dandruff proteins, 8 began to have asthma at the age of 1 year,

Assn, 1918, **70**, 897. The Cause and Treatment of Bronchial Asthma, *Med Clinics of North America*, Boston, 1918, **1**, No. 4.

5 at the age of 2 and 7 at the age 3 to 5 years, in other words, two-thirds began to have asthma previous to the age of 5 and only 2 patients began symptoms after the age of 26. Since in 9 cases the duration was from 20 to 32 years, and in 15 cases the duration was from 6 to 13 years, there is no chance for doubting the good effects resulting from horse dandruff treatment, one can hardly say that the patient outgrew, or incidentally ceased having, asthma.

Another indication of the benefit derived from desensitization with horse dandruff protein is the reduction in the positiveness of the skin test with that protein. Usually the positiveness of the skin test diminishes as the amount of protein in the treatment increases, provided the increase in the treatment is slow and gradual, if, however, treatment is rapidly increased, the skin test and the patient's desensitization cannot keep pace with the treatment and sooner or later a larger amount of protein will be given than the patient is able to stand, and consequently he may have symptoms of anaphylactic shock. If treatment is carried on for a long time and in the proper manner the positiveness of the skin test will greatly decrease and will eventually become negative. The following cases illustrate this point. Case 1 before treatment, 1:100,000 positive, after 22 treatments only 1:100 was positive, Case 2, before treatment 1:100,000 positive, after 23 treatments 1:100 positive, Case 3, 1:100,000 positive, after 41 treatments 1:100 positive, Case 4, 1:10,000 positive, after 51 treatments 1:100 negative, Case 5, 1:10,000 positive, after 20 treatments 1:100 positive, Case 6, 1:10,000 positive, after 14 treatments 1:100 positive. A total of 900 treatments has been given with the proteins of horse dandruff and to the 30 patients who were relieved of asthma a total of 675 treatments was given. It is too early to predict the duration of desensitization or the permanency of relief by such treatment, however, we do know that following a few treatments the patient is apt to relapse a few months later, but after many treatments so far no patient has relapsed. In one patient two years have elapsed, and in four others from eighteen to twenty months have elapsed without a relapse. In this research work the individual proteins in horse dandruff have been used, and it has been learned that patients vary in their degree of sensitiveness to these different proteins, and, furthermore, treatment with one of them does not desensitize against the others. The peptone and the protein are the two constituent proteins of horse dandruff that are absolutely necessary for such work, and it would seem that the other constituents are not necessary, so that for tests and treatment these two proteins should be used either separately or in equal parts together, the latter is of course the handiest to use. Patients naturally will not be so sensitive to a combination of the two proteins as to either one separately, therefore, instead of a positive skin test with a dilution

of 1 10,000 or higher, as is usually the case with either one of the proteins alone, these higher dilutions will be negative with a combination of them unless the patient is very sensitive to both

Since one might ask why nineteen patients who were sensitive to horse dandruff protein were not treated with them, a brief discussion of these cases is indicated. Five of the patients lived too far away to be available for weekly treatment. All were children or young adults, and three of them knew that exposure to horses caused asthma. Four others had attacks of asthma only when they were near horses and as these patients (all adults) were able to avoid close proximity to horses, treatment seemed to be unnecessary. Furthermore, they were not sufficiently sensitive to warrant treatment. They gave positive skin tests with the dandruff proteins in dilutions no higher than 1 100, therefore, such patients would not be exposed to enough dandruff protein in ordinary walks of life to cause trouble, the patients would have to be closely associated with horses to have trouble. Patients who are so sensitive to dandruff proteins that dilutions of 1 10,000 or 1 100,000 give a positive skin test (and this is frequently the case) we feel should be desensitized, because the dust from city streets probably contains enough dandruff protein to cause attacks in such highly sensitized individuals. Two patients, aged 23 and 28, who had had asthma for nineteen and ten years, respectively, were much more sensitive to cat hair proteins than to horse dandruff proteins, and as they did not wish to part with their pet cats, they were treated with and were relieved by cat hair proteins. One patient who had had continuous asthma for sixteen years, beginning at the of 18 months, was very sensitive to wheat proteins, and omission of wheat from the diet relieved her asthmatic condition. She knew that horses did cause her to have asthma, but she could avoid them. One patient who was not very sensitive to horse dandruff was extremely sensitive to feather protein, and he had asthma only when he slept on a feather bed. Two patients, aged 31 and 27, had had asthma for thirty and ten years, respectively, but they were not sensitive enough to be treated with horse dandruff, they were relieved by vaccines. The remaining four patients all had attacks of asthma when intimately in contact with horses, but they were not considered sensitive enough to treat, and, furthermore, on account of their bronchitis, vaccines seemed to be indicated. Their ages were 64, 63, 58 and 51, and they had had asthma for 60, 63, 7 and 20 years. In the first two cases asthma began at the ages of 1 and 4, and the first attacks in each case resulted from exposure to horses. Therefore, in all of these nineteen cases there was a definite reason for not attempting desensitization with horse dandruff protein, and yet there was enough evidence to confirm the positive skin tests with this protein.

In the whole series there were twenty patients who were sensitive to the protein in cat hair, but of this number only four were treated with cat hair protein, and of these a total of 113 treatments were given. Two of these patients were relieved by such treatment, one patient was 38 years of age and had had asthma for ten years, and the other, who was 28 years old, had had asthma for six years. The latter patient gave a positive skin test with cat hair protein in a dilution of 1 1,000,000 before treatment, and after twenty-four treatments the skin test was positive with only a 1 10,000 dilution of cat hair protein. This patient then went a year without treatment, and it is interesting that after a year without treatment the skin test was still positive with a dilution of 1 10,000, the patient has now gone a year and a half without treatment and she has been free from asthma all of this time. The first patient gave a positive skin test with cat hair proteins in a dilution of 1 100,000 before treatment, after thirty-eight treatments with cat hair protein the skin test was only slightly positive with a dilution of 1 1,000 of this protein, but the skin test remained the same for cat hair peptone, which was still positive in a dilution of 1 100,000. Twenty-three treatments were then given with cat hair peptone, and the skin test was reduced to positive with a 1 1,000 dilution. This patient shows well the specificity in the protein treatment of asthma, in that treatment with the protein alone did not change the positiveness of the skin test for peptone, and the case also shows the necessity of using both the protein and the peptone either separately or in equal parts together for tests and for treatment. Although this patient also has been free from asthma for eighteen months, treatment with the cat hair proteins is still being continued. The third treated case was that of a young girl who lived on a farm among cats and horses. Twenty treatments were given with the protein of cat hair without relief from asthma. Treatment was then begun with the protein of horse dandruff and the patient rapidly became free from asthma. Thus, this patient also well illustrates the specificity of protein treatment for asthma, since treatment with cat hair protein produced no benefit, whereas treatment with horse dandruff protein relieved the condition. The fourth treated patient was a woman, aged 42, who has had asthma for nineteen years. Since she has had only ten treatments, it is too early to prognosticate, still she has gradually improved until she is free from asthma. Therefore, of these four patients who were sensitive to and treated with cat hair protein, two were relieved, one is practically relieved during a small number of treatments, and the other, who did not improve under treatment with cat hair protein, was relieved by horse dandruff protein, so that there really were no failures either in treatment or in the skin tests.

The remaining sixteen patients, who were sensitive to cat hair proteins, were not treated with these for the following reasons. Three

patients disposed of their cats and therefore desensitization with cat protein seemed unnecessary. Three patients were sensitive to wheat and were relieved by omitting wheat from the diet. Eight patients were so much more sensitive to horse dandruff than to cat hair that they were treated with horse dandruff protein and were relieved. The remaining two patients were more sensitive to other types of proteins, although they knew that attacks of asthma had directly followed petting cats. There seems to be no evidence for doubling skin tests in these cases.

Nineteen patients were sensitive to the proteins in dog hair, but none was sensitive enough to require treatment, one patient gave a positive skin test with a dilution of 1:1,000 and all others only with a dilution of 1:100. None was sensitive to dog hair alone and all were very sensitive to horse dandruff, so that treatment was given with the latter, several were also somewhat sensitive to cat hair protein. In only two patients was there evidence that asthmatic attacks directly followed intimate contact with dogs. The infrequency of asthma from dogs and the slight degree of sensitiveness to their hair is probably explained by the fact that pet dogs are frequently bathed and are kept clean, and that the unkept street dog is not a pet, but more or less wild.

Only a rare case was sensitive to the hair of cattle, and in one instance attacks of asthma definitely followed intimate contact with cows, all of these patients were very sensitive to horse dandruff protein. The same holds true for wool. Sensitization to feather protein is fairly frequent but certainly not nearly as frequent now as in former times when feather mattresses were in vogue. In this series of cases three patients definitely had asthma from feathers, and when the feather pillows (in two cases) and feather mattress (in one case) were discarded asthma ceased. Therefore, although cattle hair, wool and feathers are not frequently the cause of asthma, yet they may be a cause, and they surely should always be considered in obscure cases.

It is thus seen that patients who are sensitive to the proteins in one type of animal hair are also frequently sensitive to the proteins in other types of animal hair. Such patients, however, are far more sensitive to some one type of animal hair than to the others, and it is with that protein to which the patient is most sensitive that treatment should be given provided the patient is not more intimately in contact with some animal hair which gave a lesser degree of sensitization. Circumstances alter cases, and treatment may be a matter of judgment. In the case of feathers and wool, avoidance of the causative agent is simpler than treatment with it, and to a certain extent this holds true for cats and dogs. It is practically impossible for one who is very sensitive to horse dandruff to avoid horses and horse dust in the street sufficiently well to prevent trouble.

Thirty patients (75 per cent of the total number of cases, and 157 per cent of the total sensitive patients) were sensitive to the protein of the cereal grains. Twenty of these were sensitive to wheat alone, 5 to wheat and other cereals together, and 5 to the cereals other than wheat. The order of frequency of sensitization to the cereals, exclusive of the 5 patients who were sensitive to all cereals, was as follows: Wheat, 20 cases, or 64 per cent; corn, 6 cases, or 20 per cent; rice, 3 cases, or 10 per cent; rye, 2 cases, or 6 per cent. Sixteen of these patients were also sensitive to other types of proteins such as animal hair, pollens or other foods, however, as the cereals contain the most common protein that enters the body, these should first be eliminated.

Of the 20 patients who were sensitive to wheat alone, 15 were relieved of asthma when wheat was omitted from the diet, all 5 of those who were sensitive to all the cereals, including wheat, were relieved of asthma when all cereals were omitted from the diet, and of the 5 patients who were sensitive to cereals other than wheat, 2 were relieved by the omission of these cereals. Therefore, in 75 per cent of the patients who were sensitive to cereals, the positive skin test was confirmed by the therapeutic test, namely, relief from symptoms when cereals were omitted from the diet. Of the patients who were relieved, 9 began to have asthma at the age of 2 years or under, and they had had asthma from 8 to 28 years, 4 began asthma between the ages of 3 and 5, and the duration of asthma was from 14 to 20 years, 6 began to have asthma in young adult life, and the duration was from 8 to 19 years, the remaining 3 patients were bakers who began to have asthma at 35, 37 and 40 years of age, and the duration was 7, 15 and 1 years, respectively. Therefore the younger the patient is when asthma begins, the more essential it is to test with the cereals, and since the duration of asthma in those relieved varied from 8 to 28 years, the relief following the omission of cereals from the diet would not seem to be accidental, or due to some other influence. Also the importance of testing bakers with the cereals is brought out.

Eight patients who gave positive skin tests with the cereals were not relieved by the omission of these from the diet. One patient, a foreigner who understood very little English, gave a positive skin test with the cereals, rye, rice and corn, but while these were omitted from the diet no improvement was noted, she was 31 years old and had had asthma for 15 years. Another patient, aged 33, who had had asthma since infancy, gave positive skin tests with wheat and corn, but she showed no benefit while these were omitted from her diet. A third patient was a baker, aged 50, who had had asthma for 9 years, he was sensitive to all of the cereals, yet the omission of these from the diet resulted in no benefit. This patient was greatly improved by

vaccine treatment Two other patients, young adults, gave positive skin tests with corn protein alone, but there was no evidence that the ingestion of corn caused trouble, and they both were relieved of symptoms by other treatment Two patients, aged 42, gave positive skin tests with only one of the wheat proteins, namely the albumin, leucosin, but with none of the other proteins of wheat One of these patients was relieved of asthma by vaccines and the other was not benefited at all, both had had asthma for twenty years The remaining patient was a young girl who had had asthma since infancy, she was sensitive to horse dandruff, wheat and egg This patient was relieved of asthma, but it is impossible to state what treatment relieved, since she omitted both wheat and egg from the diet, and at the same time was treated with horse dandruff protein It is not fair to condemn the skin test in the two cases which were positive with only wheat leucosin or in the two positive to corn alone, since these four patients might perfectly well be sensitive to these proteins but never eat them in sufficient quantities or sufficiently often to cause trouble In the three patients, however, who gave positive skin tests with several of the cereals, it must be admitted that at the present time the cereals played little or no part in the cause of their asthma and in that respect the positive skin tests were misleading, still, they should be considered as danger signals and not disregarded This point is well illustrated by a patient who gave a positive skin test with corn and oats, but these proteins did not cause asthma at that time, and asthma was relieved by vaccines, later, however, asthma returned and resisted vaccine treatment The patient was at this time eating a great deal of oats and corn in "war bread," and omission of these from the diet this time relieved the asthma

Thirty-three patients (8.25 per cent of the total, or 17 per cent of the total sensitive patients) gave positive skin tests to food proteins other than the cereals Of this number, fifteen patients gave a positive skin test with egg, seven with potato, seven with fish, five with casein, two with chicken and two with beef Occasionally a patient would be found sensitive to strawberry, spinach, peach, etc., but as these proteins were not tested routinely, it is impossible to show the relative frequency of sensitization to them Since in these patients these foods proved to be a cause of asthma, however, it may be said that probably any food protein may cause asthma

Since most of the patients in this group were sensitive to other food proteins as well as egg, potato, fish and casein, it is often hard to determine just what part these foods, which are not being eaten daily, do actually play in the cause of asthma Furthermore, the fact that many of these patients have eczema as well as asthma complicates the

interpretation of the positive skin test, but it does not detract from the value of the test

Of the fifteen patients who were sensitive to egg protein, two were relieved of asthma by the omission of egg from the diet, three others had avoided eggs since early childhood because eggs were distasteful, two patients had eczema, three were treated with and relieved by horse dandruff protein in conjunction with the omission of eggs from the diet, and the remaining five patients were also sensitive to other foods as well as egg and the omission of all of these foods relieved asthma. Therefore, it is impossible to say in just how many patients egg protein was the cause of asthma, but there is sufficient evidence to show that all of these patients were sensitive to egg, as was shown by the positive skin tests

Of the seven patients who gave a positive skin test with potato, three were relieved of asthma by the omission of potato from the diet, and two others who were also sensitive to other foods, were relieved by the omission of all of these foods from the diet. Of the five patients who were sensitive to casein, two were relieved by the omission of casein from the diet and one always had urticaria after the ingestion of milk. There were two patients who gave positive skin tests with both potato and casein in whom neither of these proteins seemed to play a part in the cause of asthma. These same two patients also gave positive skin tests with the cereals (see the foregoing), and with fish (see following), and in neither did these seem to be a cause of asthma. Therefore, it seems fairer to conclude that these two patients had a hyperirritable skin rather than to condemn the skin test

Of the seven patients who gave positive skin tests with fish protein, in four fish definitely caused asthma, in one fish caused urticaria and in the other two patients there was no evidence for a positive skin test with the exception that the patient's skin was irritable (see the foregoing). The types of fish to which the patients were sensitive were lobster, salmon, mackerel, cod, oyster and haddock. Of the two patients who were sensitive to beef, one definitely had asthma when beef was eaten and the other patient thought that she was worse when she ate beef. Both of the patients who were sensitive to chicken meat, had asthma after eating chicken and only after eating it

The relationship between the age of onset of asthma and sensitization to these food proteins shows that the younger the patient is when asthma begins the more liable is he to be sensitive to food proteins. Nine of the fifteen patients who were sensitive to egg protein, had had asthma since infancy, two others since the age of 2, and two others since the age of 3 and 4, respectively. Among the seven patients who were sensitive to potato, two had had asthma since 1 year of age, and one since 2 years of age. Among the five patients who were sensitive

to casein, two had had asthma since 1 year of age and one since 2 years of age. The remaining cases in this group began to have asthma during childhood, with the exception of the two patients who had an irritable skin, and these two were adults. With the exception of bakers, the majority of those who were sensitive to the cereals began to have asthma in early childhood.

It is noted that the treatment of those patients who were sensitized to food proteins differs from the treatment of those who were sensitive to animal hair proteins. In the latter cases desensitization was readily accomplished by the subcutaneous injection of the proteins. Those patients who were only slightly sensitive to the food proteins were satisfactorily desensitized by the subcutaneous method, but this treatment was not satisfactory in those patients who were very sensitive to the food proteins. With two patients attempts at desensitization by feeding the protein in small, gradually increasing amounts were unsuccessful because the patients (in spite of the fact that they were chosen from a large group as the most apt to follow explicit directions) did not cooperate as they should. Therefore, with the food proteins, treatment has consisted of omission of the offending food from the diet, and this has been very successful. It is not, however, the easiest matter absolutely to restrict the eating of the cereals and egg since they enter into the composition of practically all pastry and gravies, and for this reason the attention of the patient must be called to their extensive use. Another source of error as regards the cereal flours is the contamination of one grain with occasional kernels of the other grains before they are ground into flours. We have overcome this difficulty by having the patient purchase the whole grain, pick it over carefully in order to reject the few kernels which that patient should not eat, then the patient grinds the grain in his own coffee mill at home. The purchase of so-called pure flours has not been satisfactory, as many times these flours have contained ingredients which we desired to avoid, this has been especially true of rye and rice flour. Attention should be called to the fact that patients who are sensitive to corn, oat, rye and barley proteins were, before the war, eating these too infrequently and too sparingly, as a rule, to cause trouble, but since the war began these flours are being eaten so extensively that they are frequently the cause of symptoms in such cases. The duration of freedom from symptoms in these food cases depends on the length of time they are omitted from the diet. As long as they are omitted, just so long will the patient remain free from symptoms. It remains to be seen how long total abstinence is necessary to effect desensitization. It would seem, however, that total abstinence will eventually effect desensitization, since all of those who have studied infants and chil-

dren have found sensitization to egg protein in a high percentage of cases, whereas in this series of 400 cases, the majority of whom were young adults or older, there were only fifteen egg cases, or a percentage of only 3.75 per cent. It would seem plausible that many more of our patients probably, earlier in life, had been sensitive to egg and later on became desensitized, the history of distaste for certain foods is frequent and probably this is nature's way of protecting against them.

CONCLUSIONS

Of the forty-eight patients who were sensitive to and treated with horse dandruff proteins, 63 per cent were relieved of asthma, 10 per cent have had too little treatment to warrant a prognosis, and 20 per cent were relieved by vaccines or by omitting foods to which they were sensitive, in the remaining 7 per cent of this group treatment was a failure.

Of the four patients who were sensitive to and treated with cat hair protein, three were relieved of asthma, and the other patient, who was equally sensitive to the horse dandruff proteins, was relieved by treatment with them.

Of the thirty patients who were sensitive to the cereal grains, 74 per cent were relieved by the omission of these from the diet, and 7 per cent were relieved by vaccines, of the 26 per cent who were not relieved by the omission of cereals from the diet, in 16 per cent there was no evidence that cereals played any part in the cause of asthma, but the presence of eczema may account for these positive skin tests.

Of the thirty-three patients who gave positive skin tests to other foods, 50 per cent were relieved by the omission of these from the diet, 30 per cent more were relieved of asthma, but as the latter were also sensitive to other proteins which were also omitted from the diet at the same time, it is difficult to give credit to any special protein. The remaining 20 per cent were not relieved of asthma, but the presence of eczema and urticaria and an acquired distaste for certain foods probably explains the idiosyncrasy.

Therefore, of the total number of 100 sensitive individual patients who were treated as indicated by the positive skin tests, in 75 per cent there was relief from asthma, in 14 per cent, although there was no relief from asthma, there was a definite idiosyncrasy substantiating the positive skin test, but in 11 per cent the positive skin test had no apparent bearing on the patient's condition, although in only half of these, or 5 per cent, was there evidence that the skin test gave a false result. Since the 11 per cent includes 7 per cent who were relieved by vaccines, a total of 82 per cent of the sensitive patients were relieved from asthma.

THE INFLUENCE OF ACID PHOSPHATE ON THE ELIMINATION OF AMMONIA IN THE URINE¹

W McKIM MARRIOTT, M D, AND JOHN HOWLAND, M D
ST LOUIS BALTIMORE

In the course of nephritis severe acidosis may develop. Although all the usual evidences of acidosis are present, there is no increase in the ammonia of the urine. To this extent it differs from the acidosis resulting from the ingestion of strong mineral acids or from the overproduction of organic acids in the body such as β -oxybutyric and aceto-acetic acids. Henderson and Palmer¹ have pointed out that the titratable acidity of the urine in the acidosis of nephritis may be normal in amount though the total excretion of acid is low, due to "a never failing deficit in urinary ammonia." These observations would indicate that the acid responsible for the disturbance of the acid base equilibrium in nephritis is distinctly different in character from those acids causing acidosis in other conditions.

We have previously demonstrated² that an accumulation of inorganic phosphate occurs in the blood plasma of nephritics coincident with the development of acidosis. It is the failure of the kidney to excrete acid phosphate which, we believe, results in the production of acidosis.

Spiro,³ Austin and Jones⁴ and others have shown that acidosis may be caused by the administration of acid phosphate. It has not been shown why, in the presence of an undoubted acidosis, there is no increase in the urinary ammonia. It has seemed logical, therefore, to give to normal people acid phosphate and hydrochloric acid in equimolecular amounts to determine if there is a different influence on ammonia production brought about by the ingestion of these two acids.

The subjects for the experiment were four normal men, laboratory workers. Each was on his usual diet during the course of the experiments. The food intake was not controlled further than the avoidance of dietary excesses. The total nitrogen excretion in the urine from day to day indicated that the protein intake was fairly constant. The

* Submitted for publication June 18, 1918

* From the Department of Pediatrics, Johns Hopkins University

1 Palmer, W. W. and Henderson, L. J. Jour Biol Chem, 1915, **21**, 37
THE ARCHIVES INT MED, 1915, **16**, 109

2 Marriott, W McK, and Howland J THE ARCHIVES INT MED, 1916,
18, 708

3 Spiro Beitr z chem Phys u Path 1902, **1**, 269

4 Austin and Jones Am Jour Med Sc., 1917, **153**, 81

urine was collected for twenty-four-hour periods ending at 7 a. m., preserved with thymol and chloroform and kept at a low temperature

The hydrogen-ion concentration of the urine was determined by the method of Henderson and Palmer,⁵ titratable acidity by the method of Henderson and Adler,⁶ ammonia by the microchemical method of Folin and McCallum.⁷ All the above determinations were made within a few hours after the twenty-four-hour samples were complete. Total nitrogen was determined by the Kjeldahl method and phosphates by uranium titration.

The experiment continued over twelve days. There was a preliminary period of three days during which each person remained on his normal diet. During the fourth day each subject drank 500 c.c. of decinormal hydrochloric acid. The acid was all taken during the first twelve hours of the twenty-four-hour period. Following this there was another "normal" day. Then each subject took the equivalent of 500 c.c. of decinormal acid sodium phosphate (NaH_2PO_4), that is to say, the amount of acid sodium phosphate taken was such that when in solution 500 c.c. of decinormal sodium hydroxide (NaOH) were required to bring the reaction to that of the body, that is, a hydrogen-ion concentration of $10^{-7.4}$. The actual amount of acid sodium phosphate was 36.5 gm.

The following day 1,500 c.c. of decinormal acid sodium phosphate (109.5 gm.) were taken by each subject. Two "normal" days followed and then each subject took a solution of sodium phosphate having a hydrogen-ion concentration of $10^{-7.4}$ —that is the reaction of the body—and containing the same amount of phosphate (PO_4) as the 500 c.c. of decinormal acid phosphate. The following day 1,500 c.c. of decinormal neutral phosphate were taken. A subsequent "normal" day completed the experiment.

The results obtained by urinary analysis appear in the accompanying table.

Average values for some of the important factors are plotted graphically in the accompanying chart.

From the results it appears that hydrochloric acid administration increases distinctly the ammonia coefficient in the urine, the titratable acid increases in about the same proportion, so that the A/NH_3 ⁸ ratio remains essentially unchanged. That this would occur has already been demonstrated many times by others. The observation was

5 Henderson and Palmer. *Jour Biol Chem*, 1913, **13**, 393.

6 Henderson and Adler. *Proc Soc Biol Chem*, 1908, p. 38.

7 Folin and McCallum. *Jour Biol Chem*, 1912, **11**, 523.

8 A represents the total titratable acid for twenty-four hours, and NH_3 the total urinary ammonia, each expressed in cubic centimeters of decinormal solution.

RESULTS OF URINALYSIS IN AUTHORS' EXPERIMENTS

Subject	Day	Vol	T N *	P	pH	A	NH ₃	$\frac{A}{NH_3}$	
A	1	2,000	12.6	0.83	5.95	260	360	0.72	
	2	2,200	11.3	0.50	6.20	228	263	0.63	
	3	1,560	13.0	0.92	5.70	316	312	1.00	
	4	2,120	12.6	1.10	5.60	377	448	0.83	500 c c decinormal hydrochloric acid
	5	2,620	13.5	0.82	6.0	257	350	0.73	
	6	2,950	11.2	1.45	6.2	348	319	1.09	500 c c decinormal acid phosphate
	7	2,715	11.6	2.71	5.9	665	360	1.85	1,500 c c decinormal acid phosphate
	8	2,440	10.9	1.66	5.8	444	312	1.42	
	9†								
	10	3,000	9.3	1.53	6.85	210	241	0.87	500 c c decinormal neutral phosphate
	11	2,200	8.8	1.85	6.8	150	139	1.03	1,500 c c decinormal neutral phosphate
	12	2,320	12.2	1.46	6.7	270	271	1.00	
B	1	1,470	12.3	0.85	6.8	120	280	0.43	
	2	1,320	13.4	0.96	6.5	196	292	0.67	
	3	1,050	13.6	0.98	5.8	306	382	0.80	
	4	1,720	12.0	0.87	5.5	349	504	0.69	500 c c decinormal hydrochloric acid
	5	1,040	12.3	0.88	6.2	214	376	0.57	
	6	1,428	14.0	1.84	6.45	366	360	1.03	500 c c decinormal acid phosphate
	7	1,640	13.2	4.14	6.1	800	356	2.42	1,500 c c decinormal acid phosphate
	8	1,160	11.7	2.02	5.9	480	351	1.37	
	9	1,255	10.5	1.20	6.5	252	286	0.88	
	10	1,120	12.0	2.18	6.7	282	257	1.10	500 c c decinormal neutral phosphate
	11	1,575	13.1	3.58	6.85	144	197	0.73	1,500 c c decinormal neutral phosphate
	12	1,200	12.0	1.82	6.80	220	235	0.86	
C	1	1,440	16.8	1.19	6.2	300	400	0.75	
	2	1,310	15.8	1.42	5.7	420	460	0.91	
	3	1,210	16.2	1.43	5.65	456	449	1.03	
	4	1,270	16.9	1.20	5.5	496	566	0.87	500 c c decinormal hydrochloric acid
	5	1,215	15.6	1.23	5.5	440	500	0.79	
	6	1,795	21.2	2.60	5.7	604	585	1.18	500 c c decinormal acid phosphate
	7	3,920	16.4	5.40	5.5	1,400	550	2.54	1,500 c c decinormal acid phosphate
	8	1,230	12.8	2.24	5.65	612	570	1.07	
	9	1,225	14.2	1.30	5.75	370	444	0.83	
	10	1,700	12.3	2.52	6.2	556	376	1.48	500 c c decinormal neutral phosphate
	11	2,009	17.1	5.18	6.8	576	285	2.02	1,500 c c decinormal neutral phosphate
	12	2,360	15.3	2.05	6.7	370	374	1.00	

* T N = total nitrogen, grams per day, P = total inorganic phosphorus, grams per day, pH = hydrogen ion concentration of urine expressed by the negative logarithm, A = titrable acid in terms of cubic centimeters of decinormal solution, NH₃ = ammonia expressed in like manner

† Urine lost

RESULTS OF URINALYSIS IN AUTHORS' EXPERIMENTS—(Continued)

Subject	Day	Vol	TN *	P	pH	V	NH ₃	$\frac{A}{NH_3}$	
D	1	1,300	12.4	1.06	5.5	370	485	0.76	
	2	3,510	12.2	1.04	6.3	272	430	0.63	
	3	1,192	11.9	0.97	6.4	232	379	0.61	
	4	1,330	12.4	0.93	5.5	304	590	0.66	500 c c decinormal hydrochloric acid
	5	760	9.5	1.00	5.55	330	460	0.72	
	6	1,375	12.4	2.04	5.8	494	423	1.16	500 c c decinormal acid phosphate
	7	1,340	12.0	3.40	5.8	800	490	1.63	1,500 c c decinormal acid phosphate
	8	1,450	14.2	1.68	6.0	453	497	0.91	
	9	910	10.7	0.82	6.3	106	344	0.57	
	10	810	12.3	1.88	6.2	430	402	1.07	500 c c decinormal neutral phosphate
	11	1,005	12.5	3.98	6.7	420	330	1.27	1,500 c c decinormal neutral phosphate
	12	1,495	10.2	1.90	6.6	322	376	0.86	
Averages	1	1,570	13.5	0.98	6.15	262	381	0.68	
	2	2,100	13.2	1.06	6.4	279	386	0.71	
	3	1,250	13.7	1.08	5.9	328	380	0.86	
	4	1,860	13.5	1.05	5.5	404	529	0.76	500 c c decinormal hydrochloric acid
	5	1,410	12.7	0.98	5.8	310	437	0.71	
	6	1,890	14.7	1.98	6.05	476	422	1.13	500 c c decinormal acid phosphate
	7	2,400	13.3	3.91	5.8	956	439	2.17	1,500 c c decinormal acid phosphate
	8	1,570	12.4	1.88	5.85	512	433	1.19	
	9	1,130	11.8	1.11	6.1	273	358	0.76	
	10	1,660	11.5	2.03	6.5	367	319	1.14	500 c c decinormal neutral phosphate
	11	1,690	12.9	3.65	6.8	323	238	1.36	1,500 c c decinormal neutral phosphate
	12	1,860	12.4	1.81	6.7	295	319	0.93	

repeated by us for the purpose of comparison with the effect of acid phosphate on the same individuals

The administration of acid phosphate equivalent in titratable value to the hydrochloric acid, that is, 500 c c of decinormal solution, led to absolutely no increase in ammonia excretion and even three times this amount (1,500 c c of decinormal solution) also failed to increase the excretion of ammonia. There was, however, a great increase in the titratable acid of the urine, so that the A/NH_3 ratio increased greatly, reaching a point corresponding to that observed by Henderson and Palmer⁹ in severe nephritic acidosis. This difference in behavior of the phosphoric and the hydrochloric acid may be due to a difference in "strength." Equimolecular quantities of the "weak" acid phosphate

⁹ Jour Biol Chem, 1915, **21**, 37

and the "strong" hydrochloric acid should cause an equal increase in the titratable acidity of the urine, whereas a "weak" acid added to blood would neutralize bicarbonate, but would not cause as great a change in reaction as would a "strong" acid. It is this difference that may account for the failure of the weak acid phosphate to call forth ammonia.

Since the administration of 500 c c of decinormal acid phosphate is essentially the same (except for inert sodium chlorid) as the administration of an equivalent amount of neutral phosphate to which 500 c c of decinormal hydrochloric acid have been added, it would

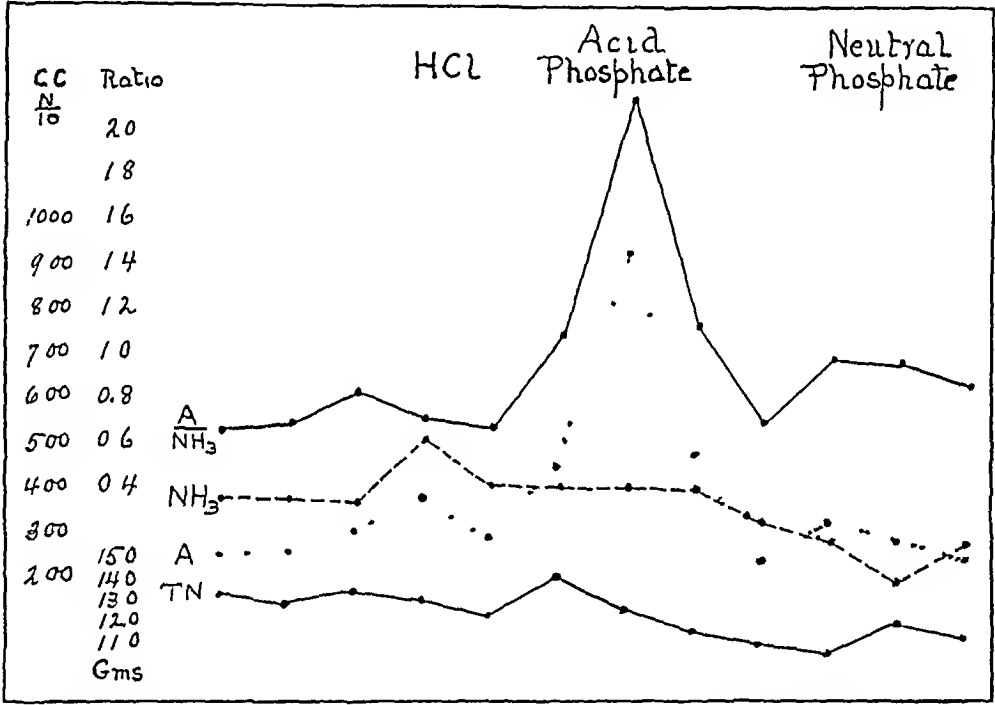


Chart showing average values of some important factors

appear that the presence of phosphate in the body actually inhibits the formation of ammonia, since hydrochloric acid alone led to a great increase. If this were true the administration of neutral phosphate, that is, phosphate at exactly the reaction of the body, should decrease the ammonia excretion of the normal subject. Our results show this to be the case. Neutral phosphate which calls for no defense of the body against either acid or alkali leads to a decrease in the excretion of ammonia, as may be seen from the table and chart. The A/NH₃ ratio becomes greater than that ordinarily seen in normal individuals.

In the presence in quantity of phosphates in the blood the addition of a strong acid would convert a portion of the phosphate into acid phosphate and this would have less effect on the hydrogen-ion concentration, and for this reason would be expected to call forth the production of less ammonia than would the strong acid in the absence

of phosphate "buffer" This may well be the explanation for the actual diminution of ammonia excretion which we have observed following the ingestion of neutral phosphate

We have previously demonstrated the retention of inorganic phosphates in the blood of nephritics with acidosis and have expressed the opinion that the acidosis depends on the retention of acid phosphate The experiments reported in this paper show that the presence of acid phosphate in the body, even in the absence of renal disease, gives rise to the excretion of urine of a character such as has been previously observed exclusively in nephritic acidosis These results, in our opinion, give additional confirmation to the view that the acidosis occurring in the course of nephritis is due to the retention of acid phosphate

BOTULISM

A FURTHER REPORT OF CASES OCCURRING IN THE PACIFIC COAST STATES ⁷

ERNEST C DICKSON, M D

SAN FRANCISCO

In a previous report¹ it was shown that prior to September, 1917, there had been twenty-two recorded outbreaks of botulism in the United States, in which eighty-one persons were poisoned and fifty-five died. In this collection of cases one important outbreak had been overlooked. In January, 1912, Dr A R McCracken² of Seattle reported a series of six cases of poisoning by home-canned asparagus, in which three of the patients died. In all, therefore, there have been at least twenty-three recorded outbreaks of botulism in this country, of which nineteen occurred in the Pacific Coast States. The mortality of these recorded cases was 66.6 per cent.

In addition to the outbreaks in which human beings were affected there were also at least six instances in which domestic fowl were poisoned and showed symptoms which were identical with those produced experimentally by feeding with the toxin of *Bacillus botulinus*.

ETIOLOGIC FACTORS

It is an important fact that, of the twenty-five instances of poisoning of human beings or domestic fowl in which the source of the poisoning was determined, seventeen were shown to have been caused by the ingestion of home-canned vegetables or fruits, and in three instances it was established that the poisoning was due to the toxin of *B. botulinus*, by the recovery of *B. botulinus* from portions of the discarded food.

Since September, 1917, there have been at least ten more outbreaks of botulism affecting human beings and four affecting domestic fowl or animals, and of these fourteen outbreaks, thirteen have been shown to be due to the ingestion of home-canned vegetables or fruits. Seven of the outbreaks affecting human beings and all of those affecting domestic animals and fowl occurred in the Pacific Coast States, and

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* From the Laboratory of Experimental Medicine, Leland Stanford Junior University School of Medicine.

* Aided by a grant from the California State Council of Defense.

1 Dickson, E. C. Botulism. The Danger of Poisoning from Vegetables Canned by the Cold-Pack Method, Jour Am Med Assn 1917, 69, 966.

2 McCracken, A. R. Botulism, Leucocyte 1912, 19, 80.

from remnants of the home-canned products which caused three of them, *B botulinus* was recovered. One of the remaining outbreaks occurred in Fallon, Nev., one in Decatur, Ind., and one in Newark, N J. I have been informed that *B botulinus* was recovered from the discarded food in two of these. It is probable that the complete report of these outbreaks will be recorded by the physicians who cared for the patients.

DANGER IN HOME CANNING OF PERISHABLE FOODS

The increase in the number of outbreaks of botulism in this country bears a very interesting relationship to the marked increase in the practice of home-canning of perishable foods which has taken place during the past few years. The home-canning of vegetables is a development of comparatively recent years, but on account of the increased cost of food products since the beginning of the war, and especially since the inauguration of the program for the conservation of foods during the past year, the amount of vegetables which are canned at home has been tremendously increased. Coincidentally with the increase in the amount of home-canning of vegetables as well as of fruits there has been a marked increase in the number of outbreaks of botulism in the United States, and it is extremely interesting that not only is there an increase in the number of instances of poisoning of human beings, but there are also more frequent occurrences of poisoning of domestic fowl and animals by feeding spoiled home-canned products (Table 1).

TABLE 1—SHOWING THE OCCURRENCE OF RECORDED OUTBREAKS OF BOTULISM DURING THE PAST NINETEEN YEARS, AND THE IMPORTANCE OF HOME-CANNED PRODUCTS AS THE CAUSE OF THE POISONING

Period From To	Interval	Number of Outbreaks		Source of Poisoning			
				Home canned		Food of Animal Origin	Unknown
		Human	Domestic*	Vegetable	Fruit		
1899 - 1903	5 years	2				2	
1904 - 1908	5 years	1	Fowl 1	1		1	
1909 - 1913	5 years	10		5†	1	3	1
1914 - Sept 1917	3¾ years	10	Fowl 5	10	1	1	3
Oct 1917 - Mar 1918	½ year	10	Fowl 3 Hog 1	10	3		1

* The outbreaks listed under "Domestic" were instances in which only fowl or animals were affected and do not include those in which human beings and fowl or animals were coincidentally poisoned.

† One outbreak was caused by commercially canned vegetables.

A REPORT OF OUTBREAKS IN WHICH HUMAN
BEINGS WERE POISONED¹

OUTBREAK 8 (three cases) —On Sunday, Nov 25, 1917, Mrs E of Seattle, opened a jar of home-canned asparagus and cooked half of the contents. None of the persons who ate the cooked asparagus suffered any ill effects. On the following evening she "warmed up" the remainder of the asparagus from the jar, by placing it for a few minutes in warm but not boiling water. Her husband stated that this asparagus did not taste very good, but he ate it all. On Tuesday afternoon Mr E complained of disturbance of vision, was nauseated and vomited. On Wednesday morning he was very weak, vomited again after taking food, and had severe diarrhea. The diarrhea continued during the day and following night, and during the night the patient complained of cramps in the legs. There was no abdominal pain during this time, and no disturbance of sensation. During Wednesday afternoon he began to have difficulty in talking. On Thursday Mr E was unable to sit up because of weakness, and he complained that he could not hold up his head. He was unable to speak intelligibly, and he complained of dryness in the mouth and pharynx. During the afternoon he began to have difficulty in swallowing, and by evening "all the water returned through his nose." He had much difficulty in clearing thick, tenacious mucus from the pharynx and had severe strangling spells when he attempted to swallow. There was no disturbance of mentality, no pain except the cramps in the legs, and no fever. He was found dead in bed early Friday morning, about two hours after he had succeeded in swallowing a small amount of milk.

On Thursday, November 29, another jar of the same lot of asparagus was opened and was served cold as salad at the Thanksgiving dinner. Two persons partook of the salad and both developed symptoms of poisoning and died. One patient was seen by Dr O F Lamson, who placed his records at my disposal. The clinical course of Dr Lamson's case was practically identical with that of the case which has been described, although there was much more severe strangling when the patient attempted to swallow. The temperature varied from 97 to 98.8 F, and the pulse from 92 to 128 per minute. The patient died on the fourth day after eating the asparagus salad.

Through the courtesy of Dr Lamson and Coroner Tiffin of Seattle, I was permitted to do partial necropsy on the bodies of two of the victims, although a coroner's necropsy had been previously performed in each case, and both bodies had been embalmed. There was moderate congestion of the meninges and of the abdominal and thoracic viscera in each case, and apparent bronchopneumonia in one. No macroscopic hemorrhages were seen. On microscopic examination a few typical thrombi were found in each case, in one occurring in the larger meningeal arteries, and in the other, occurring in the lungs. No disintegration of the Nissl granules was detected.

The remnants of the salad which had been served on Thanksgiving day were fed to the chickens, and all the chickens developed typical symptoms of limber-neck, and died. Bacteriologic examination was made of the contents of the crops and gizzards of ten of the chickens, and from six of them a virulent strain of *B. botulinus* was isolated. This strain is labeled Strain 7 of my series.

The asparagus was canned according to the directions published on page 19 of the pamphlet issued by the Kerr Glass Manufacturing Company, with the exception that it was not parboiled or blanched before it was packed in the

¹In detailing the case histories only those facts are described which are essential for establishing the diagnosis. For a more complete discussion of symptomatology and pathology refer to Dickson, E C. Botulism. A Clinical and Experimental Study. Monograph of the Rockefeller Institute for Medical Research, No 8, 1918, in which Outbreaks 1 to 7 of my series are described.

jars The material was purchased in the city market, washed in cold water, packed into 1-pint and 1-quart Mason jars which had been boiled, and covered with cold water to completely fill the jars One-half teaspoonful of salt was added to each jar and the covers were loosely applied The jars were immersed to the neck in a wash-boiler which had a tightly fitted cover, and were allowed to remain for three hours after the water began to boil actively On removal from the boiler, the jars were tightly sealed and placed in a dark closet

OUTBREAK 9 (one case) —On Wednesday, Dec 5, 1917, Miss B of Ontario, Ore, opened a jar of home-canned string beans and tasted the contents to determine whether they were good She decided that they were "not exactly right" and discarded them On the following day she complained of blurred and double vision and difficulty in articulation, and consulted Dr Rollo A Payne of Ontario, Ore, who sent me the records of the case

When Dr Payne first saw the patient there was bilateral blepharoptosis, dilatation of the pupils and difficulty in articulation There had been no nausea or vomiting, no pain and no diarrhea On the following day the blepharoptosis was more marked, speech was unintelligible and the patient was very restless, being compelled to struggle for breath There was great difficulty in swallowing Examination of the urine showed nothing abnormal, and the blood pressure was 142 mm (systolic) Miss B became rapidly worse and died about fifty-two hours after tasting the beans Dr Payne stated that the symptoms were those of a bulbar paralysis which "interfered more with the respiratory and throat muscles than with other groups" Death was apparently from respiratory failure

The discarded beans were thrown to the chickens, and thirty-nine of them died of limber-neck within two or three days after eating them

It was not possible to learn the details of the method which was followed in canning the beans

OUTBREAK 10 (two cases) —On Friday, Jan 11, 1918, Dr P M Savage of San Bernardino, Calif, was called to see Mrs J who gave the following history

On Thursday afternoon she had noticed that she "saw double," but was otherwise quite well On Friday morning she was very weak, and was scarcely able to walk, in fact, she had fallen three times while preparing breakfast Just before Dr Savage was called, the patient had staggered to a neighbor's house for help, but collapsed before reaching the door When first seen she was seated in a chair, without apparent pain, and apparently without any disturbance of mentality She complained of weakness, double vision and photophobia There was bilateral blepharoptosis, dilatation of the pupils and loss of reflex to accommodation, though not to light Articulation was very deliberate and indistinct When the patient stood she became dizzy and there was incoordination of muscular movements The skeletal reflexes were intact and there was no appreciable disturbance of sensation The temperature was 99.5 F and the pulse rate was 100

On Saturday morning there was still photophobia and double vision, and the patient complained of great fatigue There was difficulty in swallowing and the patient had severe strangling spells when she attempted to swallow During the morning articulation was distinct, although husky, but by evening speech was unintelligible During the day she became rapidly worse, swallowing became more difficult and strangling spells more frequent There was much distress from the accumulation of thick, tenacious mucus in the pharynx There was persistent constipation, but urination was not disturbed The temperature varied from 97.8 to 99.5 F, and the pulse rate from 80 to 100 The patient died early Sunday morning

Meantime on Thursday night, Miss H, a blind woman to whom Mrs J was companion, developed severe cramps in the abdomen with nausea, vomiting and diarrhea She became extremely nervous, almost hysterical, and on Friday was much fatigued During Friday night she had difficulty in swallow-

ing and by Saturday morning she strangled when she attempted to swallow. She coughed a great deal, but was unable to raise the thick, tenacious mucus from the pharynx. Articulation became difficult and speech was indistinct. There was persistent constipation after the initial diarrhea, and, except for the initial cramps, there was no pain. On account of the blindness no disturbance of vision was noted. The patient died Sunday night.

Necropsy was not obtained in either case. There was a history of both persons having eaten home-canned apricots which did not taste just right, but unfortunately the remnants of the apricots had been discarded. There was no record of the method used in canning the apricots or of the exact time at which the apricots were eaten.

OUTBREAK 11 (eight cases) —On Sunday, Jan 27, 1918, a party consisting of nine persons, five adults and four children, had supper together near Madera, Calif. The supper consisted of fresh pork, brown beans, bread, butter, milk and home-canned apricots. It was noted that the apricots had a peculiar taste, but eight of the party ate some of them. The only member of the party who escaped illness was the one who did not eat any of the apricots.

On Tuesday morning, January 29, three of the children, aged 3½, 5 and 14 years, respectively, complained of seeing double, and three of the adults complained of dizziness. The three adults also developed diplopia during the day. The fourth adult first showed symptoms of illness Tuesday night, and the smallest child, aged 13 months, became ill Wednesday evening. One of the children died Wednesday morning, January 30, two Wednesday evening and one Friday morning. Two of the adults died during the night of Thursday and the remaining two have apparently recovered after a prolonged illness.

Drs D H Ransom and St J Hely of Madera were called to care for the patients and it is to them that I am indebted for permission to study the cases, to perform necropsy in one case and to obtain various materials for bacteriologic examination.

The symptoms of all the patients were practically identical except in degree of severity. In all there were dizziness, weakness and incoordination of muscular movement, early disturbance of vision with blepharoptosis, mydriasis and diplopia, difficulty in swallowing and talking and strangling spells induced by attempts to raise thick mucus from the pharynx or to swallow. In one case, one of the patients who recovered, there was initial diarrhea and vomiting which occurred from twelve to fifteen hours before the onset of the eye symptoms, but in none of the other cases were there acute gastro-intestinal manifestations. In all the cases there was persistent constipation. The following case reports are very typical.

THREE CASE REPORTS IN DETAIL

CASE 1—*History*—F M, aged about 60, had supper with the rest of the family on Sunday evening and ate some of the apricots. He worked all day Monday, although he "felt a little out of sorts," and slept well Monday night. On Tuesday morning he was very dizzy, and, later in the day, began to see double. There was free movement of the bowels after magnesium sulphate. He again slept well Tuesday night but on Wednesday morning was very weak and uncertain in his movements, although he remained up all day. He still complained of double vision and "blurring." On Thursday morning he was so weak that he was unable to dress. There was some vertigo. For the first time the patient complained of dryness of the mouth and pharynx, and during the day he began to have difficulty in swallowing and talking. Toward evening there was much difficulty in clearing thick mucus from the pharynx, and the patient began to have severe strangling spells when he attempted to swallow. He was very restless Thursday night and slept little, although there was no pain. On Friday morning he complained of being very hungry but said he was afraid to try to swallow. He complained

of being very weak, but was able to move himself in bed with little difficulty. There had been no bowel movement for three days.

Bedside Notes—Physical examination was made by me on Friday about 10 a. m. The patient was lying comfortably in bed, apparently without pain. The temperature was 96.4 F, the pulse rate 72, and the rate of respiration 16. Respiration was not labored. Articulation was very much impaired, it was almost impossible to understand what was said, and the patient became quite irritable and stubborn when asked to repeat. He was able to raise himself in bed without difficulty and there was no apparent weakness of the muscles of the neck.

There was bilateral blepharoptosis, the pupils were dilated and reacted sluggishly to light, and the patient complained of photophobia and diplopia. There was no nystagmus. The mucous membrane of the mouth and pharynx was very dry and the tongue was swollen, heavily coated and fissured. The breath was very offensive.

Examination of the chest revealed nothing abnormal in the lungs. The area of cardiac dullness was slightly increased but the heart sounds were clear and the heart rate was not rapid. The blood pressure was 140 mm systolic and 90 mm diastolic (Tycos). The abdomen was relaxed and soft, there were no areas of tenderness, and no abnormal masses were felt. The skin was everywhere dry and somewhat atrophic.

Sensation was apparently unimpaired, mentality was clear, and the knee-jerks, plantar reflexes and biceps reflexes were normal.

Laboratory Examination—The red blood corpuscles numbered 5,300,000 and the leukocytes 16,000, of which 88 per cent were polymorphonuclear neutrophils, 9 per cent were lymphocytes, 2 per cent were mononuclears and 1 per cent eosinophils.

The urine contained neither albumin nor casts, and microscopic examination of the sediment showed no casts, red blood cells, or other abnormal constituents.

Treatment—On Friday afternoon feeding and administration of magnesium sulphate by stomach tube was commenced, and was continued until the patient was again able to swallow. Between Friday at midnight and Monday noon about 85 cc of immune goat serum were administered subcutaneously. (One cc of the serum was sufficient to neutralize approximately 3,000 minimum lethal doses of botulism toxin for a guinea-pig.) Supporting treatment was given throughout and a digitalis preparation and whisky were given when indicated. The necessary fluid was given by Murphy drip when the patient was unable to swallow.

Clinical Course—For several days the patient appeared to be very ill, was unable to swallow, talk or control muscular movements, and was very weak. He was very restless and slept little. He was frequently irritable, but was always mentally clear. The temperature varied from 97.6 to 101 F (by rectum) and the pulse rate was usually between 85 to 95 per minute.

By February 6 there began to be some signs of improvement. The patient was not so restless, he slept better, and at times was able to swallow small amounts of fluids. On February 10 he looked very much better and was able to talk more intelligibly. He stated that there had never been any pain except at the site of inoculation. The pupils were still dilated and still reacted sluggishly to light, but there was no diplopia. Bilateral ptosis persisted. The tongue was coated and very dry and fissured, but there was no longer an accumulation of mucus in the pharynx. Muscular coordination was improved, and the skeletal reflexes were normal.

Results—On March 10, six weeks after the patient had eaten the apricots, he was able to be up, to walk without staggering and "to swallow fairly well." There was no ptosis, no dilatation of the pupils and no disturbance of vision. The voice was still husky, especially after a prolonged conversation, but articu-

lation was distinct. The patient became dizzy if he attempted to move quickly, but stated that he was rapidly growing stronger and more sure of himself. There was no evidence of any persisting paralysis.

CASE 2—History—C M, aged 24, ate nothing but apricots, bread and butter for supper Sunday evening. He felt perfectly well on Monday, but on Tuesday afternoon he vomited and had diarrhea. On Wednesday he began to have double vision and dizziness, and he complained that when he tried to walk he staggered as if he were drunk. He was very restless and did not sleep well Wednesday night. On Thursday he was unable to leave his bed, and, although he was very hungry, he was unable to swallow any food. It was noted that enunciation was very difficult and indistinct.

Examination—When seen by me on Friday, there was bilateral ptosis and some photophobia but the pupils were not dilated, and they reacted fairly actively to light stimulation. The skin was dry, the tongue heavily coated and the mucous membrane of the mouth and pharynx parched. There was no congestion of the pharynx. There were no signs of impairment in the lungs and the heart was apparently normal. There was nothing abnormal in the skeletal reflexes.

There was no demonstrable disturbance of peripheral sensation, and the patient was apparently quite clear mentally, although he became irritable when he could not make himself understood. Speech at this time was almost unintelligible.

The blood pressure was 135 mm systolic and 90 mm diastolic (Tycos), and the urine showed no albumin or casts. The red blood corpuscles numbered 5,600,000 and the leukocytes 19,000, of which 80 per cent were polymorphonuclear neutrophils, 18 per cent were lymphocytes and 2 per cent were eosinophils.

Clinical Course—At first it appeared as if the patient was much less severely poisoned than his father, but gradually he became much worse, due chiefly to the fact that he had a great deal of cough and many severe strangling spells. The temperature was as high as 101 F on two occasions but usually was subnormal. The pulse rate was always above 80 and ranged between 90 and 115 for several days. On one occasion it reached 140 per minute.

Treatment—This was the same as in Case 1. The same amount of antitoxin was administered, food and laxatives were given by stomach tube and fluid was given by the Murphy drip method. A digitalis preparation was given as indicated.

Results—Recovery in this case was very slow. On March 10, six weeks after the poisoning, the patient was still confined to bed and still was forced to take his food through a stomach tube. He had become greatly emaciated and was very weak, but muscular coordination was improved and there was no ptosis or diplopia. The skeletal reflexes were normal. There had been infection at the site of inoculation of serum and small pockets of pus were still present, although bacteriologic examination failed to show any pyogenic bacteria.

CASE 3—History—B M, aged 13 months, ate very little of the fruit and did not show any symptoms of poisoning until Wednesday evening. At that time it was noted that there was bilateral blepharoptosis, mydriasis with little reaction to light, and apparent photophobia. There had not been any acute gastro-intestinal disturbance and the child did not appear to be in pain. The temperature was normal and the pulse rate 120.

Examination—When seen by me on Friday, about two hours before he died, the child was apparently conscious but very apathetic. There was marked ptosis, the pupils were widely dilated and did not react to light and the skin was very dry. The heart sounds were normal and no dulness or râles were detected in the lungs. The skeletal reflexes were normal but the muscles were

all relaxed. The temperature was 99.2 F (rectal) and the pulse rate 160. Death occurred from respiratory failure.

Necropsy Report—Necropsy was done by me about four hours after death, and before the body had been embalmed. There was marked engorgement of the vessels of the pia mater and there were a few small hemorrhages on the surface of the pons, in the space between the cerebrum and cerebellum. There was no increase in the amount of fluid in the ventricles and the cerebral convolutions were not flattened. There was no general engorgement of the abdominal and thoracic viscera but there was beginning bronchopneumonia in the bases of both lungs. The spleen was not enlarged or soft.

Microscopic examination of the tissues showed no degeneration of the ganglion cells of the brain and cord and no thrombi in the blood vessels of the central nervous system. There were well marked patches of bronchopneumonia and many masses of cellular thrombus in the larger blood vessels of the lungs. Many of the smaller vessels contained hyaline masses in which were clumps of leukocytes.

Poisoning of the Domestic Fowls—On Wednesday, April 29, the portion of the apricots which remained in the jar was thrown to the chickens. On Thursday several chickens showed symptoms of limber-neck and some of them died, and by Friday afternoon over twenty-five chickens and one turkey had died. A wild canary with similar symptoms was found lying under a tree and it died a few hours later.

Identification of B. Botulinus—Bacteriologic examination of the contents of the gizzard of one of the chickens revealed the presence of a strain of *B. botulinus* which produces a virulent toxin when grown in suitable culture mediums. This strain, which we have labeled Strain 9, was shown to produce a toxin which is homologous with Toxins 3, 4, and 7 of my series.

Methods Employed in Canning—We were unable to learn the method by which the apricots had been canned, but it is known that the fruit was unsalable, wind-fall fruit, and that Mrs. M. had marked the jars for early use as she feared the fruit would spoil. It was noted by some of those who ate the apricots that there was a peculiar sharp taste, but no unusual odor was detected.

OUTBREAK 12 (one case)—On Friday, Feb. 22, 1918, Mrs. H. of Oakdale, Calif., tasted a small portion of a bean pod from a jar of home-canned string beans which she had just opened. The beans had a peculiar irritating taste but she swallowed a small amount. When she placed the beans on the stove to cook there was an extremely disagreeable odor and she discarded them.

On Saturday morning, February 23, Mrs. H. was dizzy when she first got out of bed and she staggered when she walked. She noted that vision in the left eye was blurred. By afternoon vision was blurred in both eyes and the staggering was much worse. The patient became alarmed and consulted Dr. J. B. Thompson of Oakdale, to whom I am indebted for the following report.

When first seen by Dr. Thompson, Mrs. H. was almost hysterical but had no complaint other than that which has been detailed. She said that there had been no pain and no gastro-intestinal disturbance, and that she had not even been nauseated.

Examination showed complete dilatation of both pupils, which reacted very sluggishly to light, and a pulse rate of about 100 per minute. The temperature was normal. The patient was very weak and muscular movements were not coordinated, but nothing else abnormal was found. Dr. Thompson stated that he was strongly suspicious of belladonna poisoning, as at that time the patient denied having eaten any spoiled food.

After midnight, Saturday, Mrs. H. complained that her tongue was swollen, and she began to have difficulty in talking. On Sunday morning there was bilateral ptosis and later in the forenoon she began to have difficulty in swallowing. Speech rapidly became unintelligible. About noon on Sunday she

began to vomit and the vomiting continued for the greater part of the afternoon. There were three formed stools during Sunday forenoon and several involuntary liquid stools during the afternoon. All the stools were extremely offensive. There were no bowel movements during the last thirty-six hours of life. Toward evening on Sunday the patient began to have spells of strangling when she attempted to swallow, and she complained bitterly of the accumulation of mucus in the pharynx, which she was unable to raise. Urination was not disturbed except that the patient voided involuntarily during strangling spells.

The temperature varied from normal to 102.6 (rectal) just before death, respiration remained about 24 and the pulse varied from 98 to 120 per minute.

The patient was very restless and did not sleep during Sunday night or Monday. There was no disturbance of mentality and the skeletal reflexes were intact. There was no disturbance of sensation except a sense of numbness in the hands. She became rapidly weaker and the pulse increased in rapidity. At first there was satisfactory response to stimulation but later there was no appreciable effect. The patient died early Tuesday morning, about eighty-eight hours after tasting the beans.

To remove the mucus from the pharynx, Dr. Thompson made use of an aspiration bottle to which a soft rubber catheter was attached. He stated that this appeared to give much greater relief and to cause much less irritation than swabbing.

The beans which caused the poisoning were grown in Oakdale and were picked but a few hours before they were canned. They were washed, strung, broken into small pieces and boiled in an open kettle for twenty minutes. They were then packed into new, freshly-boiled, 1-pint economy jars, 1 tablespoonful of salt was added to each jar and the jars were covered, immersed into boiling water, which covered them, and boiled actively for three hours. Twelve jars of beans were canned and two of them spoiled. The contents of nine of the others were eaten after they had been cooked, and appeared to be good, but there is no record as to whether any one had eaten or tasted any of the beans before they were cooked. One jar was taken to the laboratory for bacteriologic examination, but no evidence of *B. botulinus* was found.

A portion of the beans from the contaminated jar was gathered from the garden where they had been thrown and had lain in the rain for several days. Bacteriologic examination showed no evidence of *B. botulinus*.

OUTBREAK 13 (one case) —On Sunday, Feb. 17, 1918, Mrs. K. of Los Angeles, opened a jar of string beans which she had canned during the past summer. She tasted four of the beans and noted that they had a peculiar taste which she at first attributed to the presence of some lemon juice which had been added to the beans when they were canned. She eventually decided that they were not good, and discarded them.

On Monday morning Mrs. K. "was distressed" and took a small dose of Epsom salts. Toward evening she vomited, and then took a large dose of Epsom salts, after which the bowels moved several times. On Tuesday she was worse, and consulted Dr. Thomas C. Myers of Los Angeles who sent me the record of the case.

When Dr. Myers first saw Mrs. K. she was extremely nervous and complained of double vision and of "swelling in the throat," dryness of the mouth and difficulty in talking and swallowing. There was marked muscular weakness and bilateral ptosis but the pupils were not dilated. The temperature was subnormal and the pulse was rapid. The patient died early Wednesday morning, about sixty hours after she had tasted the beans.

A portion of the discarded beans was recovered from the garbage can, several days after they had been discarded, but bacteriologic examination failed to show the presence of *B. botulinus*.

The beans were canned by Mrs. K. during the past summer. The exact method of canning could not be obtained, but it was known that the beans were washed, broken and packed into 1-quart, self-sealing Mason jars, and

that 1 teaspoonful of salt and "a small amount" of lemon juice were added to each jar. The jars were filled with cold water and the covers placed in position, after which they were placed in a wash-boiler and "steamed for three hours." It was impossible to find out whether the jars had been immersed in boiling water or whether they were merely steamed, nor could we learn whether the three hours was estimated from the time the jars were placed in the wash-boiler or from the time the water commenced to boil.

OUTBREAK 14 (one case) —On Sunday, March 10, 1918, Mr. A. Y. of Colton, Calif., ate home-canned pears which had a peculiar taste. On Monday afternoon he complained of a sensation of swelling of the tongue, and of vomiting. In the evening he consulted Dr. J. S. Champion of Colton, who sent me the record of the case.

Mr. Y. complained of indistinctness of vision, diplopia and vertigo and stated that he was unable to walk straight. There was some difficulty in swallowing and in talking, articulation being so indistinct that it was difficult to understand what was said. There was ptosis of the left eyelid.

There was moderately severe constipation although the bowels moved freely after the administration of Epsom salt. Diplopia and vertigo persisted for over three weeks, but after a few days the patient was able to swallow liquids, although it was impossible to swallow solids. At first there was some annoyance from an accumulation of thick mucus in the pharynx but this did not persist. The temperature ranged between 97.6 and 99.6 F., and the pulse between 60 and 112. It is interesting that the pulse rate gradually increased from 60, the rate when the patient was first seen, to 112 on the third day.

Mentality was clear throughout, but this case is of interest in that there was a persistent numbness of the left side of the body. At the end of three weeks the patient was much improved, although there were still some eye symptoms and marked weakness.

It was not possible to determine beyond a possibility of doubt that the pears were the cause of the poisoning since it is not known whether other persons partook of the same pears without suffering ill effects. Neither was it possible to learn the method which was adopted in canning the pears, but there was no record of the patient having eaten any other food which gave any indication of being spoiled.

B. REPORT OF INSTANCES IN WHICH DOMESTIC FOWL AND ANIMALS WERE POISONED BY FEEDING SPOILED, HOME-CANNED VEGETABLES

In our investigation of outbreaks of food poisoning caused by home-canned products we have obtained records of at least ten outbreaks of poisoning of domestic animals and fowl caused by feeding spoiled, home-canned vegetables. These are in addition to ten other instances in which the poisoning of the animals and fowl occurred coincidentally with outbreaks of poisoning of human beings, the animals and fowl having been poisoned by feeding them remnants of the food which had caused the poisoning of the human victims, and to several other instances in which it was believed that the poisoning was due to feeding spoiled home-canned products, although we were unable to obtain sufficiently accurate details to justify making a definite conclusion that such was the case. Six of these ten outbreaks were caused by feeding spoiled home-canned string beans, three by feeding spoiled home-canned corn and one by feeding spoiled home-canned green peas.

CAUSE OF THE POISONING CONFIRMED

The reasons for assuming that these outbreaks of poisoning of domestic animals and fowl were dependent on the presence of the toxin of *B. botulinus* in the spoiled home-canned products are the following (1) The symptoms were identical with those which occurred in animals and fowl which had been poisoned by food which had caused typical botulinus intoxication of human beings, and in which *B. botulinus* was recovered from remnants of the discarded food, (2) it has been shown that symptoms identical with those which were observed in these animals and fowl may be produced experimentally by feeding the toxin of *B. botulinus* to domestic animals and fowl,³ and (3) in one instance recorded in the following (Outbreak 1) we were able to demonstrate the presence of botulinus toxin in remnants of the mash which was fed to the chickens and to recover *B. botulinus* from the crops and gizzards of two of the chickens which died as well as from three out of six jars of the same lot of string beans which remained in the vegetable closet

Four instances of poisoning of domestic animals and fowl are detailed because of the fact that the methods by which the vegetables were canned have been ascertained

CASES OF POISONING IN DOMESTIC ANIMALS

OUTBREAK 1—On Feb 12, 1918, Mrs M of Berkeley, Calif, opened a jar of home-canned string beans and noted that they had an unpleasant odor, "something like cheese" She mixed the beans with a mash which she was preparing and fed them to the chickens Eleven of her twelve chickens developed typical symptoms of limber-neck and died

Six jars of beans which remained in the vegetable closet and the carcasses of several of the chickens as well as a portion of the mash which remained over, were taken to the laboratory for examination From the crops and gizzards of two of the chickens and from three of the jars of beans a virulent strain of *B. botulinus* was recovered, and in the mash it was found that there was still a virulent toxin present The toxicity of the beans in the jars was comparatively high, 0.001 cc of the filtered bean juice being sufficient to kill a 250 gm guinea-pig within twenty-four hours This toxin was shown to be homologous with that of Strain 6 of my series, thereby differing from all other strains which have been isolated on the Pacific Coast

The beans were grown by Mrs M in her own garden and were picked but a few hours before they were canned They were washed, broken into small pieces and packed into 1-quart Mason jars The beans were covered with cold water and were sterilized by leaving the jars immersed in boiling water in a wash-boiler for two and one-half hours on each of three consecutive days Mrs M does not remember whether the jars were sealed during the intervals

3 Dickson, E. C. Botulism A Cause of Limber-Neck in Chickens, Jour Am Vet Med Assn, 1917, 50 (New Series III), 612 Buckley and Shippin Preliminary Report on the Relation of Anaerobic Organisms to Forage Poisoning, Am Vet Med Assn, 1917, 50 (New Series III), 612 Buckley and Shippin Preliminary Report on the Relation of Anaerobic Organisms to Forage Poisoning, ibid, 1917, 50 (New Series III), 809 Graham Bruckner and Pontius Studies in Forage Poisoning V and VI, Kentucky Agricult Exper Sta, Bull 207, 1917

between sterilizations, as she had been told that it made no difference whether they were sealed or left open

OUTBREAK 2—On Feb 15, 1918, Mrs L, near Hollister, Calif, noticed that one of her hogs was dragging its hind legs and that it could not eat. On the following day the hog was down and could not get up. When disturbed it tried to squeal but was unable to do so. It remained in the same position for several days and it was noted that there had been no evacuation of the bowels during that time.

About three days later another hog became affected in the same way and Mrs L called in Dr C S Brooks of Hollister, the county veterinarian. It was through the courtesy of Dr Brooks that I was permitted to see these animals.

The symptoms of both hogs were the same, they first dragged their hind legs, eventually went down and could not rise, were unable to eat although they tried to do so, were unable to squeal and were constipated. The pupils were dilated and did not react to light, the temperature was normal and heart beat rapid. Both animals were given Epsom salt with good results. Both remained in the same condition for about one week and then gradually recovered. Within two weeks they were able to move around, to squeal and to eat.

It was learned that the hogs had been fed the contents of a jar of home-canned green peas which had spoiled and which had a very offensive odor. None of the peas were fed to chickens or to other animals.

The peas had been grown by Mrs L and had been placed in 1-quart Mason jars and sterilized by immersing the jars into boiling water in a wash-boiler for three hours. All Mrs L's vegetables had been canned by the same method and there had been a considerable amount of spoilage.

There may be some doubt as to whether the illness of the hogs was really due to poisoning with botulinus toxin as hogs are supposed to be immune to botulinus intoxication. However, the symptoms were identical with those which we have produced experimentally by subcutaneous injections of the toxins of our Strains 3 and 4 of *B botulinus*, and a virulent strain of *B botulinus* was recovered from a jar of spoiled string beans which was canned in the same way and which remained in Mrs L's cellar.

OUTBREAK 3—During the summer of 1917, Mr H of San Jacinto, Calif, canned several jars of corn by the fractional method of sterilization, in which he closely followed the instructions given in U S Department of Agriculture Farmers' Bulletin No 359. About one month later he noticed that some of the corn was spoiling and that there was gas formation. He discarded the whole lot and fed it to the chickens. Within from twelve to twenty-four hours a number of his chickens developed typical symptoms of limber-neck, and within two or three days fifty-eight out of sixty-six died. Mr H stated that he had no way of knowing whether the eight survivors had eaten any of the corn.

It was not possible to obtain material for bacteriologic examination.

OUTBREAK 4—In January, 1918, Mrs L of Raymond, Calif, threw out five jars of home-canned food which had spoiled, three 1-quart jars of peas, one 1-quart jar of string beans and one 1-pint jar of beef. The contents of all the jars had an offensive odor and were not eaten or tasted by human beings.

Within a few hours after eating the discarded food, eighty-one chickens developed typical symptoms of limber-neck and seventy-two of them died in from one to three days. Mrs L stated that the survivors had each been given a tablespoonful of castor oil.

The food was canned by Mrs L who stated that very little of her canned goods had spoiled. The material was packed in 1-quart Mason jars which had been boiled, and was cooked and sterilized by immersing the jars into boiling water in a wash-boiler for three hours.*

* This outbreak is not included in the series of ten recorded as being due to home-canned vegetables, as there is a possibility that the meat was at fault.

COMMENT

A study of these cases as well as of those described in my previous report¹ fully justifies the conclusion that the use of home-canned food is not wholly unattended with danger. In the instances which have been cited, various methods of canning were adopted and were followed as carefully as it is possible to have untrained persons conduct technical procedures. The fact that in several instances the greater part of the home-canned material remained in good condition simply proves that though the methods are efficient in preventing ordinary spoilage, they are inefficient if the raw material happens to be contaminated with spores of *B. botulinus*. It has been stated that it is essential that only freshly picked raw material should be used for canning and that it should be blanched before it is placed in the jars, but Outbreak 12 shows clearly that three hours' sterilization in the washboiler is not sufficient to kill spores of *B. botulinus* in vegetables which had been freshly picked and had been boiled for twenty minutes in an open kettle before being packed into 1-pint jars, a procedure which should be at least as efficient as simple blanching.

These cases also illustrate the fact that it is unsafe to eat or even taste home-canned products before they have been boiled. In six outbreaks of botulism the victims were poisoned by simply tasting home-canned goods to determine whether they had spoiled, and in several others the poisoning was caused by the ingestion of salads prepared from uncooked, home-canned vegetables. It is well known that the toxin of *B. botulinus* is quickly destroyed by heat and Outbreak 8 is an illustration of this fact, since those who ate the cooked asparagus on Sunday night remained in perfect health, whereas the man who ate the remainder of the asparagus from the jar, uncooked, on Monday night, developed the typical symptoms of botulinus intoxication.

It is not the object of this report to discourage the home-canning of fruits and vegetables or to interfere in any way with the active campaign for the conservation of perishable foods. It is of the utmost importance, however, that those who are directing the home-canning industry should recognize that the present methods of home-canning are not entirely safe, especially in the hands of untrained workers. If they will but admit this fact and will instruct the public that there is possible danger of poisoning from home-canned products, and that the danger may be averted if all home-canned food is boiled before it is eaten or even tasted, outbreaks of botulism from home-canned products will entirely cease.

Sacramento and Webster Streets

THE NATURE AND INTERPRETATION OF THE COLLOIDAL GOLD REACTION

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Owing to the complexity of structure and function of the central nervous system its disorders manifest themselves in clinical pictures of the utmost variety. Furthermore, in the case of one large group of these affections, the syphilitic and parasymphilitic diseases, it is highly desirable to recognize their nature as early as possible in order that the necessary treatment may be begun and the progress of the malady be arrested before destructive lesions have supervened. The difficulties of diagnosis are consequently often very great and all suitable methods of investigation yielding objective results are therefore likely to be of much assistance, particularly if they aid not only in diagnosis, but also in observing the effects of treatment. Among such procedures are the various methods of examining the cerebro-spinal fluid, such as determining the pressure under which it is held in the spinal canal, counting its cells, testing its globulin content, and carrying out the Wassermann reaction. To this list the experience of the last few years has added another, the colloidal gold reaction, and the observations so far reported indicate that it has a definite value in supplementing the information to be derived from the older sources. It is the intention here to present the results obtained in examining over two hundred cases from a general hospital service in which the colloidal gold reaction of the spinal fluid was tested over 400 times, and to compare these results with those of the other tests.

In order to understand the mode of action of the test it is necessary to step aside for a moment into the domain of the physical chemist, for the colloidal gold reaction is quite different in its principle from the ordinary test tube experiment and involves physical laws not usually called into action in the clinical laboratory.

When Thomas Graham,¹ in 1861, published his observations on colloids and crystalloids, he apparently regarded them as belonging to wholly different classes, for he said that "They appear like different worlds of matter," two fundamental distinctions being that colloids

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¹ Phil. Tr., Roy. Soc., London, 1861, 151, 183

do not crystallize, and are unable to pass through the parchment paper septum of a dialysing apparatus. Recent observations indicate, however, that the distinction is one of condition rather than of kind, for under appropriate circumstances many, if not most, substances, can be made to assume either form² and it is therefore preferable to speak simply of the colloidal state, rather than of colloids as a class. In a colloidal solution or heterogeneous system, as it is called, in distinction to the solution of a crystalloid, or homogeneous system two components or phases are recognized, the internal or dispersed phase, and the external or continuous phase. Such systems may be composed of solids, liquids, or gases in various combinations. For example, in fog a liquid is the internal phase and a gas the external phase, while in the foam on a glass of beer, the conditions are reversed. In the smoke of a cigaret a solid is dispersed in a gas, in currant jelly a liquid is dispersed in a solid, in a piece of ruby glass copper is dispersed in another solid, and finally, in the gold reagent under discussion a solid forms the internal phase and a liquid the external phase.

Evidently it is not only jellies or substances of a gluey or colloidal nature in Graham's sense that can assume the colloidal state. Solids also, that ordinarily are regarded as entirely insoluble, may be brought into a state of such minute subdivision that their particles remain suspended indefinitely in a fluid medium without settling out, and are then termed suspensoids. They have reached ultramicroscopic dimensions, and approach the molecule in size, that is, they are less in diameter than the wave lengths of the visible spectrum which lie between 700 and 400 microns. An object smaller than half the wave length of the light by which it is illuminated cannot be seen in its true form, for the light is not reflected from its surface, any more than a wave can be reflected from a pebble on the beach, and consequently a colloidal solution appears homogeneous on inspection and the particles of the suspensoid remain invisible, even with the highest magnification. When viewed with the ultramicroscope, however, in which intense lateral illumination is employed, the true nature of the system is revealed, for under these conditions even ultramicroscopic particles become visible by virtue of the Tyndall phenomenon, just as otherwise inappreciable motes may be seen dancing in a ray of sunlight entering a darkened room.

One of the ways in which colloidal solutions or heterogeneous systems differ from ordinary solutions or homogeneous systems is in the fact that in the former there are faces of contact between the external and the internal phase. Consequently the forces of surface tension

² Bayliss. *Principles of General Physiology*. London, Longmans, Green & Co., 1915, p. 109.

are brought into play, and affect the behavior of the solution. This is especially so since the area of the suspensoid has been increased to an almost unbelievable extent by its transfer to the colloidal state. A sphere of gold 2 mm in diameter has a surface of 0.126 square cm, while the surface of the same mass if reduced to colloidal particles having a diameter of 10 micromicrons would have an area of about 100 square meters, or ten million times as much.³ Siedentopf and Zsigmondy have obtained gold dispersions with particles of a diameter of less than 6 micromicrons (that is, 6 millionths of a millimeter). For comparison it may be stated that the molecules of starch are estimated to have a diameter of about 5 micromicrons, those of chloroform and of sugar about 0.8 micromicrons, those of carbon dioxide and of sodium chloride about 0.3, while the molecule of hydrogen gas, which appears to be the smallest of all, measures only about 0.1 micromicrons.⁴ Gravity has no effect on these suspended particles, which are prevented from settling out of the fluid by the action of forces akin to those responsible for the Brownian movement observed when particles large enough to be visible under high magnifications are examined in a fluid medium under the microscope. Perrin⁵ has shown that this is essentially the same as the molecular movement of the medium in which the particles are held and that it is due to the continual molecular bombardment to which they are subjected. In addition, the electrical charges of the colloidal particles are of importance, particularly in connection with their behavior when brought into contact with solutions of electrolytes. If to a colloidal system holding a suspensoid in this state of equilibrium a solution of a neutral salt, that is, containing ions in the dissociated state, is added, the colloidal particles unite to form groups or aggregates and are precipitated. This may be explained on the supposition that the ions having the opposite electric charge to the colloidal particles become concentrated on the surface of the particles and impart their charge to these, rendering them sensitive to the presence of ions of opposite charge. These in turn neutralize the charge on the particle, and cause the formation of aggregates with resultant precipitation, the effect being the greater the higher the valence, that is, the number of electrical charges, of the ion in question. Occurring on a gigantic scale, this process of flocking out of suspensoids by the action of electrolytes is responsible for the production of the Mississippi river delta through the precipitation of the colloiddally suspended particles in the turbid river water which takes place as it mixes with the highly saline waters of the Gulf, while in miniature the chemist utilizes the

3 Bayliss Principles of General Physiology, 1915, p. 89

4 Ostwald A Handbook of Colloid Chemistry Philadelphia, P. Blakistons Son and Co., 1915, p. 31

5 Perrin Comptes rend de l'Acad Française, 1908, **146**, 967

same physical forces when he obtains a water-clear filtrate from a test tube full of blood to which he has added dialyzed iron and a solution of magnesium sulphate

But still another peculiarity of colloidal solutions has to be considered before we are ready to comprehend the behavior of the reagents in the gold test. If a trace of an emulsoid or reversible colloid like gelatin is added to a solution containing a suspensoid the precipitating action of salt solutions is nullified, and the suspensoid solution is said to be in the protected state. It appears that this protective action is due to the deposition of a film of the emulsoid over each particle of the suspensoid, thus practically converting it into an emulsoid system which is no longer susceptible to flocculation by electrolytes. This principle has been made use of by Schulz and Zsigmondy⁶ in establishing a so-called gold number for the different proteins. This is the number of milligrams of the given protein required to protect 5 c c of colloidal gold from flocculation by 0.5 c c of 10 per cent sodium chlorid solution. It has been found to be a very delicate reaction, and may be used for the quantitative determination of albumins in solution, or for their identification if in pure form. The results of the gold reaction on the spinal fluid appear to depend to some extent at least on differences in the respective protective and precipitating powers of the albumin and globulin of the spinal fluid, the former acting as a protective agent and the latter as a precipitant.

After this brief excursion into the field of physical chemistry we are in a better position to understand the application of the gold reaction to the spinal fluid. The main reagent used is the gold solution, having a beautiful ruby color already familiar to everyone in the splendid hues of cathedral windows, whose wonderful glowing reds are due to colloidal gold in the glass. Faraday, in 1858, made such solutions by the reduction of gold chlorid with phosphorus and carbon disulphid, and a specimen prepared by him is still on view in the Royal Institute in London. Zsigmondy, the same investigator who developed the ultramicroscope while studying the chemistry of glass manufacture, found that better results could be obtained by using formaldehyd as the reducing agent, together with potassium carbonate,⁷ and various modifications of this method have been suggested. Through a lack of understanding of all the factors concerned, much difficulty has been experienced in obtaining proper solutions, for unless the reagent conforms to certain definite requirements it is valueless, and to secure these has been found so difficult that one author

⁶ Schulz and Zsigmondy. *Beitr. z. Chem. Phys.*, 1903, **3**, 137

⁷ Zsigmondy. *Liebig's Ann. d. Chem.*, 1898, **301**, 29, *Ztschr. f. analyt. chem.*, 1901, **40**, 697

(Glaser⁸) has gone so far as to say that owing to the uncertainty of being able to prepare a satisfactory reagent the method is unsuited for practical use, and others have described rather complicated methods of manufacture⁹

TECHNIC

Colloidal solutions of gold may be obtained in various ways, by reduction, oxidation, hydrolysis, condensation, or dispersion, the latter being effected either by chemical or by electrical means. The method that has been found most practical for the present purpose is that of reduction of gold chlorid in alkaline solution by the action of formaldehyd and oxalic acid. The reagents required are a 1 per cent solution of gold chlorid, a 2 per cent solution of potassium carbonate, a 1 per cent solution of oxalic acid, and a 25 per cent solution of formaldehyd. To make a liter of the solution, 10 cc of the 1 per cent gold chlorid solution, 7 cc of the 2 per cent potassium carbonate solution, 175 cc of the 1 per cent oxalic acid solution, and 0.83 cc of the 25 per cent formaldehyd are added to a liter of distilled water in a chemically clean flask. After thorough mixing the fluid is heated to from 80 to 85 C and kept at that temperature until a series of color changes has taken place, running through gradations from faint blue-green to a deep ruby-red. When the solution reaches its maximum depth of color a remarkable lightening in hue occurs within the space of a few seconds, the dark ruby red becoming converted to a lighter shade, and when this stage is reached, the fluid in thin layers has an orange pink color, and the reaction is finished. If the solution is properly made, 5 cc will be completely precipitated in one hour by 17 cc of a 1 per cent sodium chlorid solution, showing that it is not "protected," that is, kept from precipitation by electrolytes through the protective action of impurities. In addition, it must give characteristic results with known normal, parietic, and luetic spinal fluids. Full details in regard to a rapid and simple method for preparing the solution may be found in the *St. Luke's Hospital Guide to Laboratory Technique*¹⁰ and in an article from this laboratory by O. I. Lee.¹¹

To carry out the test, into the first of a series of eleven heavy glass, lipless test-tubes (measuring about $1\frac{1}{16}$ by 6 inches) 18 cc of 0.4 per cent sodium chlorid solution is measured and into each of the remaining ten, 1 cc of the spinal fluid to be tested, 0.2 cc is then introduced into the first tube, 1 cc of the mixture is placed in the second tube, 1 cc of this mixture in the third, and so on up to and including the tenth tube, from which, however, the 1 cc withdrawn is rejected, leaving the eleventh tube as a color control. The concentration of the spinal fluid thus ranges from 1:10 in the first tube to 1:5,120 in the tenth. To each of the eleven tubes is then added 5 cc of the colloidal gold solution and the tubes are shaken with a rotary motion to secure thorough mixing.

At the end of half an hour the color of each of the ten tubes is matched against a diffuse white background with the nearest shade selected from the color scale, using the eleventh tube for comparison.

The red or unaltered fluid is given a value of 0, red-blue 1, violet-blue 2, blue 3, pale-blue 4, colorless 5. These color values are then plotted as the

⁸ Glaser. *Neurol Centralbl*, 1914, **32**, 688.

⁹ Miller, Brush, Hammers and Felton. *Bull. Johns Hopkins Hosp*, 1915, **26**, 391.

¹⁰ Wood, F. C., Vogel, Karl M., and Famulener, L. W. *Laboratory Technique: The Methods Employed at St. Luke's Hospital*. Ed. 2. New York: James T. Dougherty, 1917, p. 86.

¹¹ Lee, O. I. A Simple Procedure for the Preparation of Colloidal Gold for Diagnostic Purposes, *Am. Jour. Med. Sc.*, 1918, **155**, 404.

abscissae against the dilutions as ordinates, so as to make a continuous curve, and this constitutes the preliminary reading. At the end of twenty-four hours the values are again read, and this is designated as the final curve, which is usually parallel to the preliminary curve, though a little higher in the scale.

Different affections of the cerebrospinal system produce changes in the spinal fluid which bring about flocking out of the gold solution in different concentrations of the spinal fluid, the varying degrees of precipitation of the gold being characterized by changes in the color of the supernatant fluid, owing to variations in the size of the aggregates of gold resulting, the color becoming bluer as the size of the particles increases. These changes have been found to be fairly consistent, so that it has been possible to establish definite curves or zones of precipitation which seem to be sufficiently reliable to permit of definite diagnostic conclusions, particularly in the case of paresis, tabes, cerebrospinal syphilis and meningitis.

We have records of over 200 cases in which the reaction was performed more than 400 times. This series is of particular interest, because in addition to the syphilitic and parasyphilitic conditions, it comprises so many others of a miscellaneous nature.

Tabes—The gold reaction is of particular interest in tabes, and of our twenty-four cases, all gave distinctly pathologic curves. The

TABLE 1—TABES DORSALIS—TWENTY-FOUR CASES

Case No	Date	Wassermann		Globulin (No. guchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
177	11/ 9/16	++--	+	0	3	1 1 152 2 2 151 0 0	Specific aortitis
	11/19/16	++++	+	0	4	1 1 2 2 2 2 2 0 0	Arterio-sclerosis
	1/ 2/17	++--	+	±	4	0 1 1 0 1 151 2 1 1	
	3/27/17	++++	0	+	8	1 1 2 2 2 2 1 0 0 0	
	5/22/17	++++	++	+	160	4 4 252 2 150 0 0 0	
178	11/ 9/16	+	++++	0	4	1 1 2 2 2 151 0 0 0	
	11/19/16	++-	++++	0	10	1 1 2 2 2 2 2 0 0 0	
	12/11/16	+++	+++	++	2	1 1 1 2 2 2 2 1 0 0	
	12/27/16			++	216	0 0 0 1 152 151 0 0	
	1/31/17	++-	++	0	2	1 1 2 2 2 0 0 0 0 0	
	2/ 2/17	----	++++	0	3	1 1 1 2 2 2 1 0 0 0	
	7/ 8/17	+	++	+	6	1 1 1 2 2 0 0 0 0 0	
	4/ 6/17	+	++	0	4	1 1 2 2 2 1 0 0 0 0	
	5/22/17	-	++	0	?	2 2 2 2 1 1 0 0 0 0	
	6/12/17	±	+-	+		1 1 1 2 1 0 0 0 0 0	
	8/14/17	+	±	±	8	1 1 2 2 0 0 0 0 0 0	
179	10/ 1/17	-	++	+	9	05051 1 05050 0 0 0	
	4 20 17	AC	-	+	9	1 2 2 2 1 1 1 1 0 0	

TABLE 1—TABES DORSALIS—TWENTY-FOUR CASES—(Continued)

Case No	Date	Wassermann		Glob- ulin (No guchi)	Lym- pho- cytes	Colloldal Gold Test	Remarks
		Blood	Spinal Fluid				
180	1/31/17	0	0	+		1 1 1 1 1 1 3 3 2 1	Previous treat- ment
	2/ 3/17	0				1 1 1 1 1 1 0 0 0 0	
	2/11/17	0	0	+	20	3 2 1 2 3 0 1 0 0 0	
181	9/19/16	+	++++	+	35	5 4 0 1 2 3 1 1 1 0	Tertiary syphilis, pyelitis, pyelo- nephrosis, gen- eral septicemia at death
	11/11/16	+		+	12	1 1 1 152 3 2 151 51	
	5/ 8/17	+++	++++	Faint+	10	1 1 1 3 2 0 1 1 0 2	
182	7/12/17	0	+++	0	4	5 2 2 4 3 2 1 0 0 0	
	7/17/17				10	4 4 4 1 4 2 151 1 0	
	9/14/17	+	0	?	10	253 4 3 2 1 0 0 0 0	
	11/ 9/17	0	++	0	3	5 4 3 252 050 0 0 0	
183	11/ 4/16	0	0	0	3	1 15152 150 0 0 0 0	Charcot joints
184	5/19/17		0	+	26	1 2 3 1 3 2 1 0 0 0	
185	1/29/17	+++	++++	0	11	2 2 2 3 2 2 0 0 0 0	Tertiary syphilis, chronic bron- chitis
	2/ 3/17		A O	0	24	1 1 2 2 3 3 2 1 0 0	
	3/ 7/17	++++	++++	0	8	1 1 2 2 3 2 1 0 0 0	
186	1/ 7/17	A O	++	+	4	1 1 2 3 3 2 1 0 0 0	
	4/13/17	0		0	15	1 2 4 3 3 1 0 0 0 0	
187	10/10/16	0	0	±	6	1 1 1 1 1 0 0 0 0 0	Cerebrospinal syphilis. Previ- ous treatment
	10/16/16	0	0	+	6	1 1 1 1 15150 0 0 0	
	11/24/16	0	0	0	4	1 2 2 2 1 0 0 0 0 0	
	1/ 9/17	0	0	0	4	1 1 1 2 1 1 0 0 0 0	
	3/17/17	0	0	0	3	1 1 2 3 1 0 0 0 0 0	
	4/24/17	±	0	0	4	1 1 2 2 2 1 0 0 0 0	
	6/ 5/17	0	0	0	4	2 2 3 3 3 1 1 0 0 0	
	7/ 5/17	0	0	0	1	1 1 2 1 0 0 0 0 0 0	
	8/17/17	0	0	0	4	1 1 1 1 0 0 0 0 0 0	
	10/13/17	0	0	+	15	1 1 1515150 0 0 0 0	
	11/13/17	0	0			1 1 0505050 0 0 0 0	
188	7/20/16	+++	++	+	24	0 1 2 152 1 0 0 0 0	Previous treat- ment
	9/19/16	+++	0	0	1	0 0 0 0 1 1 0 0 0 0	
	10/10/16	+	±	0	30	1 1 1 1 1 1 1 0 0 0	
	10/31/16	+		0	3	1 1 1 15150 0 0 0 0	
	11/21/16	+	0	Faint+	7	1 1 1 1 2 2 2 0 0 0	
	12/12/16	+++	0	Faint+	8	1 1 1 1 2 2 0 0 0 0	
	1/ 3/17	+	0	0	3	1 1 2 2 2 2 3 1 0 0	
	1/26/17	+	0	0	6	1 1 1 1 1 0 0 0 0 0	
	4/16/17	+	±	0	0	1 1 2 2 0 0 0 0 0 0	
	5/ 7/17	+	0	0	10	1 1 1 1 1 0 0 0 0 0	
	5/29/17	±	0	0	4	1 1 1 1 1 0 0 0 0 0	

TABLE 1—TABES DORSALIS—TWENTY-FOUR CASES—(Continued)

Case No	Date	Wassermann		Globulin (No guchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
189	5/24/17	0	0		1	2 3 4 3 3 2 1 0 0 0	Thrombosis of veins in right arm, cellulitis
	6/22/17		0	+	2	1 1 2 2 3 1 1 1 0 0	
190	9/18/16	+++	+++	0	11	5 5 15 1 15 15 1 0 0 0	Previous treatment
191	2/ 2/17	0	++++	0	6	2 2 2 2 3 3 2 1 0 0	Previous treatment
	2/17/17	0	++	+	4	5 2 3 4 4 3 1 0 0 0	
	3/ 9/17	0		+		1 1 2 3 4 3 1 0 0 0	
	4/11/17	±	++++	+	8	1 1 2 3 4 3 1 0 0 0	
	4/25/17	0	++	0	10	1 1 2 3 3 3 2 1 0 0	
	5/ 6/17	0	++	Faint+	12	1 1 1 2 3 2 1 1 0 0	
	6/11/17	±	++	0	10	1 1 2 1 3 1 1 0 0 0	
192	4/ 5/17	+	++++	Faint+	50	2 2 3 4 4 3 2 1 0 0	
	5/17/17	0	+	+	7	4 3 4 5 4 3 2 1 0 0	
	8/18/17	0	0			1 1 1 2 1 0 0 0 0 0	
	10/23/17	0	0	0	4	0 5 1 2 2 0 5 0 0 0 0 0	
193	7/ 3/17	++++	0	0	4	1 1 1 0 0 0 0 0 0 0	Chronic endocarditis, mitral stenosis and insufficiency Cardiac dilatation and hypertrophy Tertiary syphilis
	8/12/17	++++	0	+	20	1 1 1 2 2 0 0 0 0 0	
	8/22/17	++++	0		10	1 1 2 2 1 0 0 0 0 0	
	9/16/17	++++	0	0	9	1 1 15 2 2 1 0 0 0 0	
194	9/27/17	0	0	±	2	1 1 15 2 2 15 0 0 0 0	Previous treatment
195	12/26/16		±	+	3	1 1 2 3 4 3 2 1 0 0	
	12/31/16	+	+	++	20	0 0 0 1 1 1 15 0 0 0	
	6/ 5/17	0	±	0	8	1 1 15 15 15 1 0 15 15 15	
	7/28/17	0	0	0	7	1 1 2 2 1 0 0 0 0 0	
196	7/24/17	0?	0			1 1 1 1 2 3 2 1 0 0	
198	10/ 7/16	0	0	0	3	0 0 0 1 1 1 0 0 0 0	
	12/21/16	+	0	±	13	1 1 3 3 3 2 1 0 0 0	
	3/ 8/17	0	0	0	5	1 1 1 1 1 1 0 0 0 0	
	4/14/17	0	0	0	10	1 1 2 3 2 1 0 0 0 0	
	6/21/17	0	0	+	5	1 1 1 2 1 0 0 0 0 0	
	8/ 9/17	0	0	0	4	1 1 2 2 1 0 0 0 0 0	
	11/ 6/17	0	±	+	8	0 5 1 2 5 3 2 15 1 5 0 0	
199	3/25/17	0	+++	+	98	1 2 1 1 2 4 4 1 0 0	
201	5/27/17	0	0	0	5	1 1 2 2 2 3 2 1 0 0	
202	11/ 1/17	+++	++	+++	36	1 1 2 3 2 1 0 5 0 0 0	

curve in most cases was in the syphilitic zone, though with a tendency to be displaced somewhat to the right, and in not quite half of the cases the peak of the curve reached 4 on the color scale. In one case (No 180) one curve obtained was of the meningitic type, while a

later one was in the paretic zone, and two other patients (182 and 190) also gave paretic curves. In both of these, the Wassermann¹² was positive in both the blood and spinal fluid, but the globulin reaction was negative and the cells were not increased. Of the 24 cases, the blood Wassermann was negative in 8 and doubtful in 2, but 5 of these had already had active antisyphilitic treatment. The spinal fluid Wassermann was negative in 9, and doubtful in 1 case, and 3 of these were cases in which there had already been active treatment. The globulin reaction was negative in 5 cases, and the cells were below 10 in 5 cases. The gold reaction was therefore by far the most reliable index of the pathologic condition of the spinal fluid. In 9 cases in which repeated examinations were made at intervals while the patients were undergoing treatment by the intraspinal injection of arsphenamized serum, a distinct progressive flattening of the curves could be seen, which was in accord with the change in the clinical condition, and appears to be an objective indication of improvement which is rather more delicate than the decrease in the cells and in the globulin reaction.

Cerebrospinal Syphilis — There are 22 cases of cerebrospinal syphilis in our series. The blood Wassermann was positive in 9, negative in 7, and doubtful in 4 cases, and in 2 the reaction was not determined. The spinal fluid Wassermann was positive in 15, negative in 5, and doubtful in 2 cases. The globulin reaction was positive in 19 and negative in 3 cases, and the cells were over 10 in 13, and 10 or under in 9 cases. The gold reaction was pathologic in all cases but 2, though the average elevation of the peak was not quite so high as that in tabes. In the latter condition 4 or over in the color scale was reached in 46 per cent of the cases, and 3 or over in 83 per cent, while in cerebrospinal syphilis the respective figures are 31 per cent and 72 per cent. The distinction, however, has not very much differential diagnostic value. In two cases the gold curve was only of the irritation type, that is, with no tube showing a color value greater than 1.5. In both of these the globulin reaction was positive, in one the blood Wassermann was positive, but the spinal fluid Wassermann was negative, while in the other, the spinal fluid Wassermann was positive and the blood Wassermann was not tested. Here again the gold reaction appears to be the most reliable single test, though the globulin reaction is little behind it in value.

12 The Wassermann reactions were performed under the direction of Dr L. W. Famulener. The technic included the use of an antishoop hemolytic system and waterbath fixation. Two antigens were used, namely, the Noguchi acetone-insoluble, and alcoholic extract of guinea-pig heart, and in each case the reaction was performed in duplicate with two different specimens of antigen.

TABLE 2—CEREBROSPINAL SYPHILIS—TWENTY-TWO CASES

Case No	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
105	5/17/17	0	+	+	80	1 1 1 1 1 2 2 1 1 1	
	6/ 1/17	0	0	+		1 2 3 2 2 2 0 0 0 0	
	6/21/17	0	0	+	1	1 2 3 2 2 2 0 0 0 0	
	9/13/17	0	0		7	1 152 2 1 0 0 0 0 0	
106	8/29/17	++++	++++	0	3	1 1 1 2 3 3 2 1 1 0	
	9/ 8/17	++++	++++	+	4	1 1 1 15152 1 1 0 0	
	9/16/17				6	1 2 253 3 2 2 0 0 0	
107	6/19/17	0	+++	+	50	2 3 3 3 2 1 1 0 0 0	
	8/10/17	0	0	+	12	1 2 3 3 2 1 0 0 0 0	
108	11/ 7/16	0	0	0	1	1 15151 1 0 0 0 0 0	
	12/ 3/16			Faint+	14	1 1 1 1 1 1 0 0 0 0	
	1/ 9/17	0	0	0	3	1 1 1 1 0 0 0 0 0 0	
	2/10/17	±	0	0	9	2 2 1 1 1 0 0 0 0 0	
	3/ 2/17	0	0	0	2	1 1 1 1 1 0 0 0 0 0	
	3/16/17	0	0	Faint+	6	1 2 2 2 1 1 0 0 0 0	
	8/10/17	0	0	+	20	2 2 1 1 0 0 0 0 0 0	
	10/ 4/16	+	0	+	12	0 0 0 0 0 0 0 0 0 0	
109	11/ 7/16	0		0	1	0 1 1 1 0 0 0 0 0 0	
	12/14/16			0	4	1 1 1 1 1 1 0 0 0 0	
	2/ 6/17	0	0			1 1 1 0 0 0 0 0 0 0	
	3/11/17	0	0	0	3	1 1 1 0 0 0 0 0 0 0	
	4/11/17	±	+++		5	1 2 3 2 1 0 0 0 0 0	
	6/ 5/17	0	0	0	4	0 0 1 1 0 1 1 1 1 1	
	7/ 1/17	0	0	?	4	1 1 1 2 1 0 0 0 0 0	
	8/17/17	0	0		8	1 1 1 0 0 0 0 0 0 0	
110	8/ 9/17	0	0	0	3	1 2 2 1 0 0 0 0 0 0	
	8/12/17	0		0	7	1 1 1 2 0 0 0 0 0 0	
	9/30/17	0	0	0	3	1 2 2 2 2 1 0 0 0 0	
	11/ 3/17	±	0	0	5	051 2 1505050 0 0 0	
111	3/22/17	0	±	0	4	1 1 2 3 2 1 0 0 0 0	
112	3/ 1/17	++++	++	+	24	1 1 1 2 3 2 2 1 0 0	Chronic nephritis
113	6/ 1/17	0	++	++	10	1 1 1 1 152 3 151 0	Tumor of spinal cord
	6/ 5/17		+	+	6	5 5 3 3 4 3 3 1 1 0	
114	7/27/17		++	++	200	5 1 1 2 3 4 2 0 0 0	
	7/31/17					1 1 2 3 3 2 1 0 0 0	
	8/14/17		+++			1 1 3 4 2 2 1 0 0 0	
	10/17/17		+			1 1 152 15150 0 0 0	

TABLE 2—CEREBROSPINAL SYPHILIS—TWENTY-TWO CASES—(Continued)

Case No	Date	Wassermann		Globulin (No guchu)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
115	1/24/17	++++	++	0	6	1 1 2 3 3 2 0 0 0 0	Tabes dorsalis(?), tertiary syphilis, progressive muscular atrophy
	2/ 1/17	++++	++	0	12	1 1 1 3 2 1 0 1 0 0	
	2/10/17	+++	++	+	14	1 2 3 4 3 1 1 0 0 0	
	2/24/17	+	0	+		1 1 2 3 2 1 0 0 0 0	
117	11/17/16	++++		0	5	1 1 1 2 3 2 2 1 1 0	Chronic rheumatoid arthritis. Previous treatment
	12/15/16	+++	+++	0	5	1 1 1 2 2 3 2 1 1 0	
118	1/31/17		+++	+	10	1 1 1 1 1 1 0 0 0 0	
119	1/ 4/17	0	++	0	6	1 1 1 3 4 3 2 0 0 0	
	2/28/17			0	3	1 1 2 3 3 3 2 1 0 0	
	5/13/17	0				3 1 3 3 4 3 2 1 0 0	
	11/ 9/17	0	++	0	4	1 1 1 0 50 50 0 0 0 0	
120	4/ 5/17	A C	A C	+	50	1 2 3 4 3 2 1 0 0 0	
121	7/11/17	0	0	0	8	1 2 3 2 2 0 0 0 0 0	
	7/25/17	0	0	0	12	1 2 2 3 1 0 0 0 0 0	
	8/ 7/17	0	0	+	15	1 2 2 2 1 0 0 0 0 0	
	11/28/17	0	0	0	3	2 2 2 1 0 0 0 0 0 0	
122	8/24/17	++++	++++	?	10	0 5 4 3 2 1 51 1 0 0	
	8/29/17	++++	++++	?	15	1 1 2 3 4 3 1 1 0 0	
	10/31/17	++++	++++	+	9	1 1 52 2 1 50 0 0 0 0	
	12/ 2/17	+++	++++	+	13	1 2 2 2 1 50 50 50 0 0	
123	3/22/17	0	++++	+		1 1 2 4 3 1 0 1 2 2	
	5/23/17	0	+++	0	9	5 4 1 53 53 3 1 51 0 0	
	7/31/17			Faint+	5	1 1 2 3 2 3 0 0 0 0	
	9/20/17	0	+	?	5	0 50 51 2 2 1 0 0 0 0	
124	9/25/16					0 0 0 0 0 0 0 0 0 0	
	10/24/16	0		+	3	0 0 0 0 0 0 0 0 0 0	
	11/22/16			+	18	1 1 1 1 1 1 0 0 0 0	
	1/ 2/17	+	0	0	5	0 0 0 0 0 0 0 0 0 0	
	4/ 3/17	+	0 ⁹	0	3	1 1 1 2 0 0 0 0 0 0	
	6/ 1/17	+	0	0	8	1 1 1 1 1 0 0 0 0 0	
	8/13/17	+	0	+		1 1 1 1 0 0 0 0 0 0	
	10/13/17	+	0	+	36	0 50 50 51 1 0 0 0 0 0	
	11/14/17	+	0	++	15	0 0 0 0 0 0 0 0 0 0	
125	11/17/17	±	++	++	9	1 1 1 1 1 0 0 0 0 0	
	11/28/17	0	++		3	1 2 2 2 1 0 50 0 0 0	
126	11/ 1/17	++++	0	+	30	0 50 50 50 50 50 0 0 0 0	
127	10/15/17	+ ⁹	+++	++++	11	1 1 1 1 51 52 0 0 0 0	Cerebral gumma, tertiary syphilis
	11/ 2/17	±	+++	++++	120	0 51 1 52 3 1 51 50 0 0	
	11/12/17	++++	+++			1 1 51 51 52 1 51 0 0 0	
	11/28/17	+++	+			1 52 2 2 1 0 50 0 0 0	

Paresis—In the group clinically diagnosed as paresis, comprising 6 cases, the blood Wassermann was negative in 1, the spinal fluid Wassermann in 2, and the cells under 10 in 2 cases, while the gold curve was of the irritation type in 1 instance In 2 cases the curve was of the syphilitic type, once with both Wassermann reactions posi-

TABLE 3—GENERAL PARESIS—SIX CASES

Case No	Date	Wassermann		Glob- ulin (No guchl)	Lym pho cytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
203	9/16/16	+++-	++++	+	6	4 4 3 52 1 1 1 0 0 0	Tertiary syphilis
	9/29/16	++++	++++	+	5	5 4 1 2 2 2 150 0 0	
	10/16/16	++++	++++	+	16	1 51 1 52 3 3 150 0 0	
	11/ 7/16	+++-	++++	+	12	4 2 2 3 2 2 0 0 0 0	
	11/25/16	++++	++++	++	12	3 3 2 2 2 2 0 0 0 0	
	12/16/16	++++	++++	+		2 2 2 3 3 3 1 0 0 0	
	1/ 5/17	++++	++++	+	6	1 1 2 4 3 2 1 1 0 0	
	2/ 3/17	++-	++++	0	3	2 2 1 1 1 1 0 0 0 0	
	3/ 6/17	++++	++-	+	50	1 1 2 3 4 3 1 1 0 0	
	4/ 7/17	++++	++++	+	40	3 2 2 1 0 0 0 0 0 0	
	5/ 8/17	++-	++-	+	34	1 1 2 3 3 2 3 0 0 0	
	6/19/17	++	++	++	350	1 2 2 3 3 2 0 0 0 0	
204	1/ 9/17	±	0	0	6	1 1 1 1 1 0 0 0 0 0	Previous treatment
205	6/ 7/17	++-	++++	+		5 3 3 4 4 3 3 1 1 0	
	6/21/17	++-	++-	+	7	5 5 3 4 4 1 1 0 1 0	
206	7/21/16	A C	+++-	+	8	5 5 5 5 5 5 5 2 150	
	7/26/16	++-	++++	+	11	5 5 5 5 5 151 0 0 0	
	11/ 5/16	++++	+++-	+	14	5 5 5 5 5 5 5 150 0	Syphilitic aortitis with aortic and mitral regurgitation, cardiac hypertrophy
	11/22/16	++-	++++	++	36	4 4 4 4 4 4 3 51 51 0	
207	11/16/16	0	0	+	15	1 1 1 51 51 51 1 0 0 0	
	11/20/16		0	++	20	1 1 1 2 2 2 0 0 0 0	
208	9/26/16	+	++-	+	9	1 1 1 53 2 1 50 0 0 0	
	10/10/16	0	++-	0	12	1 1 1 1 1 51 1 0 0 0	
	12/ 8/16	±	+++	++?	12	1 2 3 3 3 2 2 0 0 0	
	1/10/17	0	0	0	6	1 1 1 2 1 1 0 0 0 0	

tive and once with both negative, but the others gave the characteristic paretic high level for the left hand tubes

Tertiary Syphilis—Of tertiary syphilis there are 24 cases in the series In all of these, except one (No 145), the Wassermann was positive in either the blood or spinal fluid or both, and in this case there had been active antisyphilitic treatment The blood Wassermann

TABLE 4—TERTIARY SYPHILIS—TWENTY-TWO CASES

Case No	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
128	11/15/16	+	0	0		1 1 1 2 2 1 1 0 0 0	Aortitis with aortic regurgitation, splenomegaly (syphilitic?), leukemia?
129	8/29/17	0	0	0	6	1 1 1 1 0 0 0 0 0 0	Intestinal intoxication
130	2/ 1/17	++++	0	+	17	1 1 1 2 3 2 1 0 0 0	Cervical fibroid, pedunculated
131	11/ 3/16	++++	0	0	3	1 1 5 1 5 1 5 1 0 0 0 0	
132	1/25/17	++++	0	0	9	1 1 2 2 1 1 0 0 0 0	Optic neuritis
133	6/ 1/17	++++	++++	++++	42	2 2 5 3 3 3 1 1 0 0	Spastic paraplegia
	6/ 5/17	+++	+++			2 3 3 2 2 1 0 0 0 0	
	6/14/17	+++	+++			1 2 2 3 1 1 0 0 0 0	
	7/22/17	+	+	0	7	1 1 1 1 0 0 0 0 0 0	
	8/15/17	±	+			1 1 2 1 0 0 0 0 0 0	
134	4/ 5/17		0	+	10	1 2 3 4 3 2 1 0 0 0	
135	12/ 3/16	0	++?	++?	7	1 1 2 2 2 2 1 0 0 0	Previous treatment
	2/10/17	0	++	0	5	1 2 2 3 3 1 0 0 0 0	
	8/20/17	0				1 1 1 2 1 0 0 0 0 0	
136	11/ 4/16	+++	0	0	8	1 1 5 2 2 2 0 0 0 0	Pulmonary tuberculosis, chronic gumma of brain
137	12/ 9/16	++++	0	++	13	1 1 1 2 2 2 1 0 0 0	
	12/17/16		0?	+	2	1 1 1 1 2 2 1 0 0 0	
138	10/13/16	+	0	0	3	1 1 1 1 5 1 5 1 0 0 0 0	Syphilitic hepatitis (gumma?), pelvic laceration
139	9/22/17	++++	0	?	8	0 5 0 5 0 5 0 5 0 0 0 0	
140	11/ 9/16	++++	0	0	2	1 1 1 1 1 0 0 0 0 0	
	3/18/17	++++	0	0	8	1 1 1 2 1 0 0 0 0 0	
	7/ 9/17	++++	0	0	1	1 1 1 1 1 0 0 0 0 0	
141	7/26/17	+	+	+	10	1 1 2 2 2 1 0 0 0 0	
142	11/16/16	+	0	+	20	1 1 1 1 0 0 0 0 0 0	
143	1/19/17	++++	0	0	8	1 1 1 1 1 0 0 0 0 0	Aneurysm of aorta (arch)
144	10/25/16	+	0	0	3	1 1 1 1 5 1 5 1 5 1 5 0 0 0	Syphilitic aortitis, chronic endocarditis, salvarsan poisoning
145	12/ 2/16	0		+	7	1 1 1 2 2 1 0 0 0 0	"Salvarsan arm"
146	11/18/16	++++	0			1 1 1 1 1 0 0 2 0 0	
148	10/30/17	+++	0	0	2	1 1 1 1 0 0 0 0 0 0	Cholelithiasis?
149	9/10/17	+	0	0	7	1 1 1 5 1 5 1 0 0 0 0 0	
150	1/23/17	++++	0			1 1 1 1 1 1 1 0 0 0	

was positive in 16 cases, negative in 5 cases, and in another was not performed. The spinal fluid Wassermann was positive in 3 cases, was negative in 17, and was not performed in 2 cases. The globulin test was positive in 9 cases, negative in 10, and in 3 instances was not

made The cells were 10 or under in 18 cases, and above 10 in 4 cases The gold curve was in the syphilitic zone in 11 cases, and of the irritation type in 11 Of the 16 cases giving a positive blood Wassermann, 5 gave a negative spinal fluid Wassermann (Nos 128, 130, 132, 136 and 137) but a gold curve in the syphilitic zone In these 5 cases

TABLE 5—ACUTE ANTERIOR POLIOMYELITIS—THREE CASES

Case No	Date	Lymphocytes	Poly-nuclear Leukocytes	Globulin (Noguchi)*	Colloidal Gold Test
170	7/20/16	4	0	0	5 4 2 1 0 0 0 0 0 0
171	6/ 9/17	6	0	+	1 1 1 2 3 1 1 1 0 0
172	6/ 8/17	3	0	Faint +	1 1 2 1 0 0 0 0 0 0

* The Wassermann reactions on blood and spinal fluid were negative in every case

TABLE 6—CONGENITAL SYPHILIS—FOUR CASES

Case No	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Colloidal Gold Test	Remarks
		Blood	Spinal Fluid				
173	8/29/17		0*	0	4	1 1 1 1 1 0 0 0 0 0	
174	9/10/17		0	?	8	1 1 1 1 0 0 0 0 0 0	
	11/11/17	++++	0?	0	4	0 0 0 0 0 0 0 0 0 0	
175	2/21/17		++++	+	30	1 1 2 2 1 0 0 0 0 0	
	3/15/17	++++	A O	+	9	1 2 3 2 1 1 0 0 0 0	
	5/27/17	+	±	+	5	1 2 3 3 2 2 0 0 0 0	
	7/ 1/17		0	0	4	1 2 3 2 1 1 0 0 0 0	
	9/23/17			0	4	1 1 1 0 50 50 0 0 0 0	
	10/27/17		±		5	1 1 1 1 0 0 0 0 0 0	
176	10/ 9/16	+	0			1 1 1 1 1 0 0 0 0 0	
	1/ 6/17	±	0	0	2	1 1 2 2 1 0 0 0 0 0	
	5/13/17		0?	0	6	2 2 2 2 1 1 0 0 0 0	
	6/22/17	0	0	0	8	1 1 2 2 0 0 0 0 0 0	
	8/31/17	0	0	0	3	1 1 1 51 50 0 0 0 0 0	
	11/11/17	0	0	0	4	1 1 0 0 1 0 0 0 0 0	

* +++++ before treatment

the globulin reaction was positive only twice This indicates one of the most important uses of the gold reaction It appears to be a more delicate index of syphilitic change in the spinal fluid than the Wassermann and the globulin test, and it is therefore of value in detecting the earliest onset of cerebrospinal lesions The importance of this in the prophylaxis of the parasymphilitic diseases is evident,

TABLE 7—TUBERCULOUS MENINGITIS—NINE CASES

Case No	Date	Lymphocytes	Poly-nuclear Leukocytes	Globulin* (No guchi)	Colloidal Gold Reaction	Remarks
152	7/18/16	188	20	++	0 15 2 3 35 4 4 35 3 0	Pulmonary tuberculosis
	7/19/17	281	29	0	1 1 15 15 15 15 1 1 15 0	
	7/21/16	140	0	+++	1 5 4 15 1 0 0 0 0 0	
153	1/30/17	81	0	+	1 1 1 2 2 2 0 0 0 0	
154	8/ 6/17	30	1,470	+	1 1 2 2 1 0 0 0 0 0	
	8/ 9/17	90	210	+	4 1 3 2 1 0 0 0 0 0	
	8/10/17	324	486	+	1 1 1 1 2 3 1 3 0 0	
155	8/ 9/17	344	56	+	1 1 1 2 2 0 0 0 0 0	
156	12/ 5/16	171	9	++	1 1 2 2 2 2 1 1 0 0	
	12/ 6/17	303	12	++	1 1 1 1 2 2 2 1 0 0	
	12/10/16	182	15	++	1 1 1 2 3 3 2 1 0 0	
157	11/20/16	450	0	++++	1 1 1 1 2 3 3 3 0 0	
158	6/26/17	90	0	+	1 1 1 2 2 1 1 0 0 0	
159	6/29/17	88	0	+	1 1 1 1 3 3 1 2 0 0	
	7/ 2/17	98	0	+	1 2 1 3 3 4 2 2 0 0	
74	12/ 2/16	126	0	+	1 1 1 2 2 2 0 0 0 0	
	12/ 5/16	316	16	++	1 1 1 1 2 2 1 1 0 0	

* The Wassermann reaction was negative in every case in which it was performed

TABLE 8—MENINGITIS—TEN CASES

Case No	Date	Lymphocytes	Poly-nuclear Leukocytes	Globulin* (No guchi)	Colloidal Gold Test	Remarks
160	7/ 8/17	4	0	0	1 2 3 3 1 0 0 0 0 0	Serous meningitis
	7/16/17	4	0	0	1 1 2 2 2 1 0 0 0 0	
161	5/15/17	1,360	5,440	+	1 1 1 1 1 2 3 0 0 0	Epidemic cerebrospinal meningitis
162	5/15/17	440	660	+	0 0 0 0 1 150 0 1 1	Epidemic cerebrospinal meningitis
163	12/21/16	152	8	++	0 0 0 0 0 1 2 1 3 1	Lobar pneumonia, influenza
164	3/ 4/17	38	342	+	0 0 0 0 0 2 4 2 2 1	Pneumococcus meningitis, lobar pneumonia
165	4/24/17	140	1,260	+	0 0 0 0 0 0 0 1 152	Acute purulent meningitis (pneumococcus), ethmoiditis, purulent
166	5/28/17	3,750	8,750	+++	0 150 0 0 152 151 1	Epidemic cerebrospinal meningitis
167	11/17/16	267	513	++++	0 1 1 1 1 1 3 4 4 3	Septic meningitis (pneumococcus)
168	3/22/17	280	120	+	1 1 2 3 3 2 0 0 0 0	Cerebrospinal meningitis
	4/ 6/17	1,400	0	+	2 2 3 4 3 2 1 0 0 0	
169	1/22/17	64	1	+	1 1 1 2 1 0 0 0 0 0	
	1/23/17	12	0	±	1 1 1 1 1 0 0 0 0 0	Acute septic meningitis

* In every case in which the Wassermann reaction was performed it was negative

and every syphilitic with a positive blood Wassermann should have the colloidal gold reaction done on the spinal fluid in order that proper treatment may be begun at a stage before permanent organic lesions have developed

Three cases of poliomyelitis gave a pathologic gold curve in each instance, though the cells were below 10 in all three, and in one case the globulin reaction was negative. In one case the curve was in the paretic zone, and in the other two, it was of the syphilitic type

Four cases of congenital syphilis are recorded. Of these, three gave positive blood Wassermanns, and one gave a positive spinal fluid Wassermann. Two of the cases gave a gold curve in the syphilitic zone, while two, both with negative spinal fluid Wassermann reactions, gave only irritation curves

There are nine cases of tuberculous meningitis. These all gave curves chiefly in the syphilitic zone. Of ten other cases of non-tuberculous meningitis, all except one case of epidemic cerebrospinal meningitis gave curves which for the most part are characterized by a displacement to the right, which is typical of acute meningeal inflammation. One case is of interest because, although the cell count and the globulin reaction were both negative, so that the diagnosis of serous meningitis was made, the gold curve was a well marked one

We have records of tests in 102 cases of miscellaneous conditions, in many of which pathologic curves were obtained, though not with sufficient regularity to be of definite diagnostic value. For example, of 12 cases of chronic nephritis, 7 gave only irritation curves, while in 4 cases accompanied by uremia, there was a well marked elevation in the syphilitic zone. In one of these the spinal fluid Wassermann was positive, though the cell count and globulin reaction were negative. In another case, there was complete flocking out of the gold in 7 of the 10 tubes. Of 5 cases of hysteria, 4 gave only irritation curves, but 1 with a positive globulin reaction and negative blood and spinal fluid Wassermann gave a syphilitic curve. Out of 3 cases of multiple sclerosis 1 was negative, another with positive blood and spinal fluid Wassermann, globulin reaction, and increased cell count gave first a syphilitic curve and ten days later a paretic curve. A third case in which the diagnosis was somewhat in doubt gave a syphilitic curve, though the blood and spinal fluid Wassermann, globulin, and cell count were all negative. In 2 cases diagnosed as neurasthenia there were curves in the syphilitic zone, though the blood and spinal fluid Wassermann, cell count, and globulin reaction were all negative, which is of interest as indicating a possible organic basis for the symptoms. One of the two cases of epilepsy gave a negative curve, and the other a syphilitic curve though the other reactions were all negative. Three of the 4 cases of chorea gave negative curves, and the fourth a low

TABLE 9—MISCELLANEOUS CONDITIONS—104 CASES

Case No	Date	Wassermann		Globulin (No gucin)	Lymphocytes	Polynuclear Leukocytes	Colloidal Gold Test	Diagnosis
		Blood	Spinal Fluid					
6	4/16/17	0	+++	0	4	0	1 1 2 3 2 2 1 0 0 0	Chronic diffuse nephritis, uremia
9	8/ 7/17	0	0	0	3	0	1 1 1 2 1 0 0 0 0 0	Chronic nephritis uremia diabetes mellitus
12	10/24/16	0	0	0	3	0	1 1 1 1 1 0 0 0 0 0	Chronic diffuse nephritis, acute endocarditis, mitral insufficiency, right pleurisy with effusion
14	5/ 2/17	0	0	0	4	0	1 1 1 1 0 0 0 0 0 0	Chronic nephritis
19	7/30/17	0	0				1 1 1 1 2 3 3 1 0 0	Chronic nephritis, uremia, cystic adenoma of breast, colloid goiter, cerebral hemorrhage, fibroids of uterus
30	11/ 6/16	0	0	+	7	0	5 5 4 4 4 5 5 5 5 5	Chronic interstitial nephritis, cardiac hypertrophy, cerebral sclerosis, left hemiplegia
77	12/10/16	0	0	0	3	0	1 1 2 3 3 3 2 1 0 0	Chronic nephritis, arterio sclerosis, hypertension
78	2/16/17	±	0	0	5	0	1 1 1 1 0 0 0 0 0 0	Chronic nephritis, transitory uremia
88	5/26/17	0	0	0	6	0	1 1 1 1 1 0 0 0 0 0	Chronic nephritis, eczema
99	10/21/17	0	0	0	4	0	0 50 50 50 50 0 0 0 0 0	Chronic diffuse nephritis hypertension, cardiac hypertrophy
100	11/14/17	++++	0	0	8	0	0 50 50 50 50 50 0 0 0 0	Nephritis, chronic endocarditis
103	10/30/17	0	0				1 1 1 1 50 50 0 0 0 0	Chronic nephritis, pulmonary tuberculosis
8	4/29/17	0	0	0	5	0	1 1 2 2 1 1 0 0 0 0	Hysteria
42	9/28/17	±	±	0	6	0	1 1 52 151 0 0 0 0 0	Hysteria
55	6/17/17	0	0	0	3	0	0 0 0 0 0 0 0 0 0 0	Hysteria
84	9/18/17	0		0	7	0	0 50 50 50 0 0 0 0 0 0	Hysteria
97	4/ 2/17	0	0	+	10	0	1 1 2 2 1 0 0 0 0 0	Hysteria
	4/14/17	0			10	0	1 1 1 2 2 1 0 0 0 0	
4	10/ 5/17	0	0	0	4	0	1 1 52 52 52 0 0 0 0 0	Multiple sclerosis ?
17	4/ 3/17	0	0	+	3	0	0 0 0 0 0 0 0 0 0 0	Migraine
30	9/ 6/17	0	0	0	3	0	1 1 1 1 1 0 0 0 0 0	Epilepsy
31	4/14/17	0	0	0	3	0	1 1 2 2 2 1 1 0 0 0	Neurasthenia
33	2/ 7/17	A C	0	0	6	0	1 1 2 3 3 2 0 0 0 0	Hematomyelia, transverse myelitis
	2/16/17	A C	0	+	17	0	3 1 3 2 3 4 3 2 0 0	
34	6/26/17		0	++	30	0	1 1 1 1 1 1 1 0 0 0	Poli-encephalitis
43	11/12/16	0	0	0	4	0	1 1 1 1 0 0 0 0 0 0	Chorea
	11/20/16		0				1 1 1 2 1 0 0 0 0 0	
48	10/ 6/17	0	0	0			1 1 151 51 50 0 0 0 0	Chorea
	10/16/17		0	0	6	0	0 50 50 50 50 50 0 0 0 0	
52	7/ 5/16	+	0				151 1 1 1 1 1 1 1 1	Transverse myelitis (syphilitic?)
61	7/26/17	0	0	?	7	0	1 1 1 1 0 0 0 0 0 0	Psychoneurosis
65	4/22/17	0	0	0	2	0	1 1 2 3 3 1 0 0 0 0	Neurasthenia, toxic neuritis
66	9/28/17	0?	0	0	3	0	1 1 151 0 0 0 0 0 0	Headache

TABLE 9—MISCELLANEOUS CONDITIONS—104 CASES—(Continued)

Case No	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Polynuclear Leukocytes	Colloidal Gold Test	Diagnosis
		Blood	Spinal Fluid					
72	12/ 7/16	0	0	0	3	0	1 1 1 2 2 1 0 0 0 0	Chronic alcoholism with edema of brain, pleurisy with effusion, pulmonary tuberculosis
76	12/10/16	0	0	0	6	0	1 1 2 2 2 1 0 0 0 0	Sciatica
13	6/ 5/17	0	0	+	12	0	1 1 2 3 2 2 0 0 0 0	Alcoholic neuritis, delirium tremens
79	7/24/17	0	0	+	128	2	1 1 1 0 0 0 0 0 0 0	Chorea
	8/ 2/17		0	0	3	0	1 1 1 0 0 0 0 0 0 0	
80	6/16/17	0	0				1 1 1 2 2 0 0 0 0 0	Functional neurosis
81	11/ 3/16	0	0	0	4	0	1 1 1 1 1 1 0 0 0 0	Alcoholic neuritis
	11/ 7/16			0	3	0	1 1 1 15150 0 0 0 0	
	11/13/16			0	6	0	1 1 1 1 0 0 0 0 0 0	
82	7/27/17	0	0	?	10	0	1 1 1 2 1 1 0 0 0 0	Paralysis due to toxic agent
86	10/17/16			0	6	0	0 0 0 0 0 0 0 0 0 0	Chronic chorea
	11/14/17				6	0	1 1 1 0 0 0 0 0 0 0	
94	7/15/17	0	0	0	4	0	1 1 1 1 1 1 0 0 0 0	Traumatic neurosis
101	11/15/17	+++	+++	++	23	0	1 153 2 15050 0 0 0	Multiple sclerosis
	11/25/17	+++	+++	++	13	0	5 5 4 3 252 1 0 0 0	
102	11/17/17	0	0	+++	7	0	0 0 0 0 0 0 0 0 0 0	Multiple sclerosis?
7	6/29/17	0	0	+	6	0	1 1 1 1 2 2 2 1 0 0	Cerebral tumor
5	1/18/17	0	0				1 1 1 1 2 2 1 0 0 0	Cerebral hemorrhage, glaucoma
23	5/14/17		0	0	3	0	0 0 0 0 0 0 0 0 0 0	Hemiplegia
26	2/10/17	0	0	+	8	0	1 1 1 2 2 1 0 0 0 0	Hemiplegia
28	9/11/17	0	0	0	4	0	151 1 1 1 0 0 0 0 0	Hemiplegia
36	6/23/17	0	0	+	4	0	0 0 0 0 0 0 0 0 0 0	Partial left hemiplegia; multiple cerebral softening
93	1/15/17	0	0	+	108	0	1 1 1 2 2 1 0 0 0 0	Hemiplegia
50	10/ 3/17	0	0	0	5	0	051 1 1 0 0 0 0 0 0	Spastic paraplegia (lateral sclerosis?), secondary anemia
63	4/ 1/17	0	0	0			1 1 1 1 0 0 0 0 0 0	Neuralgia of fifth facial nerve
90	3/30/17	0	0	0	6	0	1 1 2 2 1 0 0 0 0 0	Epilepsy, Pott's disease
32	11/14/16	0	0	+	8	0	1 1 1 1 1 1 1 0 0 0	Chronic alcoholism
40	6/11/17	0	0	0	4	0	1 1 1 1 1 0 0 0 0 0	Alcoholic neuritis
70	11/24/16	0	0	+	15	0	1 1 1 2 2 2 1 0 0 0	Brain tumor
	11/30/16	0	0				1 1 1 2 2 2 1 0 0 0	
	12/ 7/16	0	0	+	9	0	1 1 1 2 2 2 1 0 0 0	
	12/10/16	0	0	++	32	0	1 1 1 2 2 3 1 0 0 0	
	12/21/16	0	0	+	15	0	1 1 1 2 3 2 1 1 0 0	
	1/ 3/17	0	0	0	6	0	1 1 1 2 2 2 3 2 0 0	
10	1/ 8/17	0	0	0	5	0	1 1 1 2 2 1 0 0 0 0	Chronic myocarditis

TABLE 9—MISCELLANEOUS CONDITIONS—104 CASES—(Continued)

Case No	Date	Wassermann		Globulin (No-guchi)	Lymphocytes	Polynuclear Leukocytes	Colloidal Gold Test	Diagnosis
		Blood	Spinal Fluid					
19	5/21/17	0	0	0	3	0	1 1 2 3 2 1 1 0 0 0	Aortic aneurysm
21	10/10/17	0		0	5	0	1 1 1 15 1 1 0 0 0 0	Chronic myocarditis
37	8/ 7/17	0	0	0	4	0	0 0 0 0 0 0 0 0 0 0	Chronic endocarditis, chorea
41	9/10/17	++++	0	0	6	0	0 0 0 0 0 0 0 0 0 0	Chronic endocarditis
45	7/27/17	0	0	0	8	0	1 1 1 0 0 0 0 0 0 0	Chronic cardiac valvular disease, chronic cardiac insufficiency, chronic dilatation, aortitis, manic depressive psychosis
57	10/ 8/17	0	0	0	5	0	1 1 1 15 15 15 0 0 0 0	Endocarditis
62	7/19/17	0	0	0	2	0	0 0 0 0 0 0 0 0 0 0	Aortic aneurysm of arch arteriosclerosis and hypertension
87	5/28/17	++++	0	0	2	0	1 1 2 2 3 2 1 0 0 0	Aortic aneurysm, celiac axis aneurysm
89	5/30/17	0	0	0	16	0	1 2 3 2 2 1 0 0 0 0	Paroxysmal tachycardia
18	5/22/17		0	0	10	0	1 1 1 2 1 0 0 0 0 0	Lobar pneumonia
29	2/ 1/17	0	0	0	12	0	1 1 1 1 1 1 0 0 0 0	Lobar pneumonia
	2/ 2/17	0	0	0	8	0	0 0 0 0 0 0 0 0 0 0	
	2/ 4/17			0	5	0	1 1 1 1 0 0 0 0 0 0	
69	4/13/17			0	5	0	1 1 2 2 2 2 0 0 0 0	Lobar pneumonia
92	6/23/17	0	0	+	45	0	0 0 0 0 0 0 0 0 0 0	Lobar pneumonia
38	5/11/17		0	0	4	0	1 1 1 1 0 0 0 0 0 0	Bronchopneumonia, otitis media
14	6/ 9/17	0		+	10	0	1 2 2 1 0 0 0 0 0 0	Acute bronchitis, chronic emphysema
75	11/ 8/16	0	0	0	7	0	1 15 2 2 15 15 0 0 0 0	Acute miliary tuberculosis
1	1/22/17	0		0	4	0	1 2 2 2 0 0 0 0 0 0	Phimosis, mental deficiency
2	7/ 7/17	0	0	0	4	0	1 2 2 3 1 1 0 0 0 0	Intestinal intoxication, arteriosclerosis, hypertension, pyelitis, aortitis
3	1/30/17	0	0	0	3	0	0 0 0 0 0 0 0 0 0 0	Chronic iritis
11	2/26/17	0		0	3	0	1 1 1 2 1 1 1 0 0 0	Acromegaly
15	8/27/17	0	0	0	7	0	2 2 1 1 0 0 0 0 0 0	Acute gastro enteritis
16	12/15/16	0					1 1 1 1 1 1 3 1 0 0	Hydrocephalus
20	4/16/17	0	0	+	2	0	1 1 2 1 0 0 0 0 0 0	Recurrent carcinoma of uterus, pelvic and spinal (?) metastases
22	3/11/17	0	0	0	5	0	1 1 1 1 1 0 0 0 0 0	Goldthwaite's disease
24	1/11/17	0	0	0	3	0	1 1 1 2 1 1 0 0 0 0	subluxation of sacro iliac joint
25	2/28/17		0	0	5	0	0 0 0 0 0 0 0 0 0 0	Hypertension
27	3/26/17	0	0	+		0	1 1 1 2 3 0 0 0 0 0	Uveitis, posterior synchiae, panophthalmitis, neurasthenia
35	10/29/16	0	0	0	1	0	1 1 1 15 15 0 0 0 0	Ischio rectal abscess
39	6/13/17	0	0	+	4	0	1 1 1 1 0 0 0 0 0 0	Menopause
								Tumor of right brachial artery

TABLE 9—MISCELLANEOUS CONDITIONS—104 CASES—(Continued)

Case No	Date	Wassermann		Globulin (Noguchi)	Lymphocytes	Polynuclear Leukocytes	Colloidal Gold Test	Diagnosis
		Blood	Spinal Fluid					
46	5/28/17	0	0		20	0	1 1 1 2 0 0 0 0 0 0	Iliac thrombosis, pelvic tumor?
	8/15/17		0				1 1 1 0 0 0 0 0 0 0	
47	9/22/17	0	0	0	3	0	0 50 50 50 50 0 0 0 0 0	Gastric neurosis and flatulence, gonorrheal cervicitis
51	1/26/17	0	0	0	6	0	1 1 1 1 0 0 0 0 0 2	Chronic gastritis
53	11/30/16	0	0	0	9	0	1 1 1 1 1 0 0 0 0 0	Retroversion, fibroid (?), uterus
54	5/21/17	0	0		2	0	1 1 1 2 1 1 1 0 0 0	Chronic septic arthritis, hip
56	10/10/16	0	0	++	8	0	0 0 0 1 1 0 0 0 0 0	Endarteritis (syphilitic ?) spinal cord
58	10/19/16		0	+++	20	0	0 0 0 0 1 1 15 15 1 0	Sarcoma, right popliteal region, spinal cord metastasis
59	12/16/16	0	0	0	3	0	1 1 2 2 2 1 1 0 0 0	Gastric ulcer
	6/29/17	0	0				1 1 1 2 1 1 2 0 0 0	
64	7/13/17	0	0	0	3	0	1 2 2 1 0 0 0 0 0 0	Chronic cholecystitis
67	7/ 9/17	0	0	+	6	0	1 1 2 3 2 0 0 0 0 0	Acute epididymitis
68	10/15/16	0	0	0	3	0	1 1 1 15 15 0 0 0 0 0	Carcinoma of stomach
71	3/21/17			+	10	0	1 1 1 1 1 1 1 0 0 0	Congenital polycystic kidneys, acute uremia
73	10/25/16	0	0		8	0	0 0 1 15 15 15 0 0 0 0	Splenomegaly
	11/ 7/17	0	0		1	1	1 1 15 2 2 15 1 0 0 0	
	11/13/16	+	0	+	8	0	1 1 1 15 2 15 1 0 0 0	
	11/16/16	0	0	+	21	4	1 1 1 15 2 2 2 1 1 0	
	11/29/16	0	0	+	15	0	1 1 1 2 3 3 1 0 0 0	
	1/30/17		0	+	3	0	1 1 1 1 1 1 1 0 0 0	
83	8/23/17	0		0	3	0	1 1 1 0 0 0 0 0 0 0	Acute enteritis
85	2/22/17		0	+	4	8	1 1 1 1 0 0 0 0 0 0	Fractures, base of skull, and leg
91	10/ 8/17		0	0	3	0	0 1 15 15 1 0 0 0 0 0	Duodenal ulcer
95	7/ 7/17	++++	0	+	6	0	1 1 2 1 0 0 0 0 0 0	Acute rheumatic fever
96	9/25/16	0	0	0	4	0	0 0 0 0 0 0 0 0 0 0	Chronic otitis media, epilepsy (?)
98	10/ 5/17	0?	0	0	4	0	1 2 2 5 3 1 0 0 0 0 0	Carcinoma of liver
104	10/31/17	0	0	+	7	0	0 50 50 51 1 0 50 0 0 0	Chronic infective arthritis

syphilitic curve, the other tests being negative. One case of transverse myelitis gave only an irritation curve, and another a syphilitic curve, the other tests being negative. There were 5 cases of chronic alcoholism. Two of these, one in which the diagnosis of edema of the brain was made, and the other with delirium tremens, gave syphilitic curves, though the Wassermann reactions were negative, but 3 cases with peripheral neuritis gave only irritation curves. Two cases of brain tumor with positive globulin reactions, but negative Wassermann reactions, gave curves showing a slight displacement to the right. Of 5 cases of hemiplegia, 3 gave negative curves and 2 syphilitic

curves, though the Wassermann tests were negative. A curious observation was that in a case of paroxysmal tachycardia there were 16 cells per cubic millimeter and the gold curve was in the syphilitic zone, though the Wassermanns were negative.

In comparing the gold curve and the spinal fluid Wassermann the following may be said. In our series comprising 24 cases of tabes, 22 of cerebrospinal syphilis, 22 of tertiary syphilis, 6 of general paresis and 4 of congenital syphilis, or 78 altogether, there were no instances in which at the first examination the spinal fluid Wassermann was positive but the gold curve was negative. There were two cases, however, in which the spinal fluid Wassermann was positive and the curve was under two in the scale at the first examination. These were both cases of cerebrospinal syphilis, and in one (No 118) only a single examination was made, but in the other (No 125), although the first examination gave a curve under two, a later one showed a good syphilitic reaction.

On the other hand, in these 78 cases there were 33 in which at the first examination the spinal fluid Wassermann was negative, but the gold curve was pathologic in character. In 16 of these cases the curve reached 2 or over in the scale, and it is particularly interesting to note that 7 of these instances occurred in cases of tabes.

CONCLUSIONS

1 It must be emphasized that each of the different tests on the spinal fluid is of value only as a single factor in the entire examination, and that no one test alone is pathognomonic.

2 The colloidal gold reaction is the most sensitive indicator we have of pathologic changes in the spinal fluid, the globulin reaction closely approaching it in delicacy.

3 Uremia, neurasthenia, serous meningitis, hemiplegia and chronic alcoholism may give a curve in the syphilitic zone.

4 If the gold reaction is negative, it is highly probable that the spinal fluid Wassermann will also be negative.

5 An important application of the gold reaction is in the recognition of the earliest stages of cerebrospinal syphilis, and its routine employment in all syphilitics is to be recommended as an aid in the prophylaxis of the parasymphilitic diseases.

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A CLINICAL STUDY OF ONE HUNDRED AND FIFTY CASES OF BRONCHIAL ASTHMA[†]

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Within the past few years, there has been a growing interest in the association and relation between anaphylaxis and asthma. The original theories of this relation have been often discussed.

This growing interest has served to emphasize the important point that the diagnosis of bronchial asthma is only the first step in the diagnosis of the absolute cause of the particular patient's difficulty.

The writer's purpose in this present work has been to determine the cause of asthma in the 150 patients who form the basis of this report and, if possible, to arrange these patients in groups. These 150 patients were seen in the out-patient department and wards of the Massachusetts General Hospital, and a few outside the hospital.

Each patient had been previously studied by a competent internist. Organic lesions of the heart, lungs and blood as a cause of dyspnea, had been considered and ruled out, often only after sputum examinations and roentgen-ray examinations of the chest had been made.

Each patient gave a history of attacks of shortness of breath accompanied by wheezy respiration, for which attacks no obvious cause could be found by the ordinary clinical examination.

In each case, the diagnosis of asthma had been made previously, and on this account the patient was referred to the writer. Such diagnoses were accepted without further study.

ETIOLOGIC FACTORS

The prevalent and generally accepted theory today is, as Meltzer¹ originally pointed out, that asthma is a clinical manifestation of anaphylaxis, that these patients with asthma are sensitized to various foreign proteins which are either inspired or ingested from without the body or absorbed from some focus of infection or suppuration within the body. The cases in this report have been studied in the light of this theory.

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¹ Meltzer, S. J. Anaphylaxis and Asthma, Jour Am Med Assn, 1910, 55, 1021.

The medical literature of recent years is full of attempts to find the cause of asthma. The work of Walker is especially brilliant and the reader is referred to his original papers,² and to his excellent summary³ for full details.

Asthma from inhalations of horse hair,² plant pollens,² feather dust,² etc., from eating of eggs,⁴ berries,⁵ fish,⁶ cereals,⁷ etc., are all known, and such cases will be referred to in the present paper as having an extrinsic cause of their asthma. Intrinsic causes are also well recognized, that is, where the cause lies within the patient's body. For example, there is much literature dealing with the relation of pathologic conditions in the nose and throat to asthma.

Grant⁸ summarizes the findings in his 107 cases, and records improvement or cures of asthma in forty-five out of fifty-nine cases treated for nasal disease. Abbott,⁹ Gottlieb¹⁰ and Bonnier¹¹ all consider the nose and throat and local treatment directed to it, as being important. Matthews¹² from the Mayo Clinic says that in over 90 per cent of the cases the principal etiologic lesions are in the upper respiratory tracts, and that treatment is successful in proportion as free and continuous drainage is obtained.

The cases of Davies¹³ illustrate other intrinsic causes where the asthma was apparently relieved by the appropriate treatment of such conditions as uterine displacement, undescended testicle, abdominal ptosis, constipation, dysmenorrhea, etc., and where, because of this relief, the author claimed an etiologic relationship between these conditions and the asthma.

Hare¹⁴ has seen asthma associated with malaria, migraine, epilepsy, Raynaud's disease, etc.

2 Walker, I C. Studies in Bronchial Asthma, Jour Med Research, 1917, **31**, 243.

3 Walker, I C. Studies on the Cause and the Treatment of Bronchial Asthma, Jour Am Med Assn, 1917, **69**, 363.

4 Schloss, O M. Am Jour Dis Child, 1912, **14**, 341.

5 Frost, L C. A Case of Intense Food Anaphylaxis, Med Rec, New York, 1915, **88**, 483.

6 Muhsam and Jacobson. Deutsch med Wchnschr, 1914, **40**, 1067.

7 Smith, H R. THE ARCHIVES INT MED, 1909, **3**, 350.

8 Grant, Dundes. Nasal Disease in Relation to Asthma, Practitioner, Lond 1913, **90**, 914.

9 Abbott, W J. Bronchial Asthma and the Relation of Nasal Conditions to It, Am Jour Otol, Rhin and Laryngol, 1914, **33**, 83.

10 Gottlieb. Etiology and Treatment of Bronchial Asthma, New York Med Jour, 1917, **106**, 313.

11 Bonnier. Arch gén de méd, Paris, **91**, 197.

12 Matthews, J. Med Rec, New York, 1914, **84**, 507.

13 Davies, B C. A Clinical Study of Asthma, Jour Am Med Assn, 1914, **62**, 1006.

14 Hare, F. Varieties and Treatment of Asthma, Brit Med Jour, 1911, **2**, 1442.

Babcock's case¹⁵ is also interesting in which the asthmatic attacks were definitely related to cessation of drainage from an infected gall-bladder

Jackson¹⁶ has distinguished two types of experimental asthma, (1) that due to stimulation of the broncho-constricting muscles directly, and (2) the type due to the stimulation of the nerves to these muscles. He does not indicate more remote causes or attempt to group cases, his work being done entirely with animals

It is worth while here to review briefly some of the facts of experimental anaphylaxis. A sensitized guinea-pig will react always to a parenteral introduction of the protein or proteins to which he is sensitized, this reaction being either local or general according to the dose and method of administration. He will not react to other proteins, the reaction is thus highly specific. The reaction takes place at once and its intensity varies with the size of the reinjection dose. In case of recovery, the guinea-pig will not again react to the same foreign protein until after a certain latent period.

When, on the other hand, we come to study critically many cases of asthma, we find that most of these well recognized postulates of experimental anaphylaxis do not obtain. But there are certain obvious differences.

In the first place, we are dealing with man and not animals. In the second place, we are dealing with cases of natural sensitization and, as Dr. Longcope¹⁷ has pointed out, there are many differences between this and artificial sensitization, for as he showed, in naturally sensitive men, the susceptibility is very great, reactions often of violent character being readily produced by minute quantities of the particular proteid, the susceptibility is often shown toward several proteins at once and is, therefore, multiple, and finally, natural sensitiveness has a tendency to occur in families.

One method of demonstrating this sensitiveness or susceptibility is by the use of the skin test.

The fact that persons who are sensitive to proteins give a local reaction to the application of that protein in the skin was brought out as long ago as 1910 by Moss,¹⁸ who also found¹⁹ that artificially sensi-

15 Babcock, R. H. The Nature and Treatment of Bronchial Asthma, *Jour Am Med Assn*, 1915, **64**, 2115

16 Jackson, D. E. Pharmacology of Bronchial Asthma, *Jour Lab and Clin Med*, 1915, **1**, 126

17 Longcope, W. T. Susceptibility of Man to Foreign Proteins, *Am Jour Med Sc*, 1916, **152**, 625

18 Moss. *Jour Am Med Assn*, 1910, **55**, 776

19 Knox, Moss and Brown. Subcutaneous Reactions of Rabbits to Horse Serum, *Jour Exper Med*, 1910, **12**, 562

tized rabbits develop a positive skin test to the original protein after an incubation period of from seven to ten days

Since then, and especially in recent years, the skin test has had wide usage, when its application to the diagnosis of hay fever, horse asthma and many other conditions thought to be dependent on an anaphylactic background has been frequent and usually satisfactory

SCOPE OF THIS REPORT

The cases in this report are essentially adults, more than half of them began to have asthma when they were past the age of 20

The individual cases in this report have been studied as follows. A careful history has been obtained in each case, the particular object being to discover the conditions and circumstances related to the attacks of asthma

A complete physical examination has been made, including in most cases an examination of the nose and throat by an expert, and in many cases a roentgenogram of the chest

Skin tests have been studied in nearly all the patients. In this work the intradermal method, by which definite amounts of protein are injected between the layers of the skin, has been used exclusively. The proteins used have been various animal serums, solutions of egg-white and extracts of plant pollens, of animal hairs, and of fish muscle, different combinations being used according to the history and findings in the individual cases. These protein solutions were all standardized according to their total nitrogen content, were sterile, and gave no reaction in the skin of normal control individuals

In the performance of these tests, each protein except the various animal serums, was diluted with 0.9 per cent salt solution containing 0.5 per cent carbolic acid, so that each cubic centimeter of the resulting solution contained 0.02 mg of total nitrogen. In this way it has been possible to compare the various local reactions one with another in as accurate a way as possible. The animal serums were each diluted 1:100

The tests have invariably been performed on the outer aspect of the upper arm beginning at the tip of the olecranon process. The 0.25 cc pipet-syringes described by Terry²⁰ have been found very convenient for making the intradermal injections, as they can be sterilized by dry heat, are then ready for instant use, and can be easily transported. An injection of carbolized salt solution was always given as a control.

The typical positive reaction consists of an urticarial wheal which appears usually within five minutes and within fifteen minutes reaches often from 12 to 16 mm and occasionally from 50 to 60 mm in

20 Terry, M. C. Precision Syringes, *Jour Infect Dis*, 1913, **13**, 80

diameter. It has sharply defined, steep borders. Very characteristic are the pseudopodia-like projections which extend out in all directions making very grotesque figures. A bright pink areola with fairly sharp border is almost always present, but the criterion of a positive test has been the enlarging wheal and not this areola.

In many cases, in which a series of tests have been done, the arm will present a row of elevated macules each measuring from 8 to 12 mm with a relatively small well defined and often mottled areola around each, the areola measuring, perhaps, from 15 to 30 mm—the test with plain carbolyzed salt solution giving the same appearance. There are no pseudopodia and the wheal does not enlarge as fast as does the areola. Such results have been interpreted as showing that the skin of that particular person was such that any test solution might act purely as an irritant. Such tests have obviously been discounted in the diagnosis.

More rarely, perhaps only a half of the test solutions showed this “irritative” reaction, these reactions have been all discounted.

It should be said that there are often all transitions between the true “anaphylactic” reactions and these irritative reactions, and that the differentiation and interpretation is often difficult. The cases of definite susceptibility, however, almost never fail to give a true reaction to the specific protein.

Great stress has been laid on these skin tests only when results obtained were compatible with the patient's history. For example, if a patient gave a positive skin test to ragweed pollen extract and yet had asthma throughout the year, the test was more or less disregarded unless it so happened that there was a definite aggravation of symptoms during the hay fever season.

Skin tests were done on a total of 127 out of 150 cases. One or more tests were positive in 74 cases (50 per cent), and of these 74 positive tests, 40 (in 27 per cent of the cases) were compatible with the patient's history, and under these conditions the diagnosis, or at least one factor in the diagnosis, was assumed to be proved.

In this way these cases have been arranged in groups.

Effort has been made to keep in touch with as many patients as possible, to see if the course of their asthma proved to be consistent with the original impression and classification of the case.

Before considering the individual groups, it should be noted that asthmatic individuals fall into two great divisions according to whether their asthma depends on the susceptibility to foreign proteins without the body (extrinsic), or whether their asthma depends on the theoretical absorption of foreign, in this case probably bacterial, protein from within the body (intrinsic).

DIFFERENTIATION OF CASES

In order to aid in the differentiation between extrinsic and intrinsic cases, stress has been laid on three special points

(1) *On the Family History*—Longcope in particular has brought out the hereditary tendency of natural sensitiveness Cooke²¹ found in his 621 cases of sensitization a positive family history on one side in 205 cases, and a positive on both sides in 39 cases, or a positive family history in 48 per cent of his cases of hay fever, which, as he says, is in striking contrast to the 14.5 per cent of positive antecedent histories in seventy-six normal persons

Talbot²² finds a positive family history in all of the 19 cases of asthma in children which he studied in great detail The fact that patients with asthma or hay fever are more likely to recognize similar disease in their relatives than people not suffering from this disease is obvious

It should here be said that most of the cases in this report are from the out-patient class, and as such do not often give competent answers Furthermore, they have asthma The relation of family history to different groups of asthma will be discussed later

(2) *On the Eosinophilia*—It is known that foreign protein acts as an eosinotactic substance while bacteria seem to repel the eosinophil cells (Staubli²³)

Furthermore, according to the Ehrlich-Lazarus conception,²⁴ eosinophilia occurs whenever epithelial or cellular destruction goes on, and as Schlecht says, it is of favorable significance insofar as it is an expression of a reaction from foreign protein that has entered the body, or from native protein abnormally broken up inside the body

Eosinophilia can be artificially produced in animals by the injection of foreign protein substances (Staubli,²⁵ Schlecht²⁶ and Proscher²⁷)

And in man, after an injection of diphtheria antitoxin, there is a rise of eosinophils, which rise depends on the amount of serum injected (Schlecht²⁷)

If a sensitized animal is reinjected, there is at first a local eosino-

21 Cooke, R. A., and Vander Veer Human Sensitization, Jour Immunol, 1916, **1**, 201

22 Talbot, F. B. Asthma in Children, Etc., Boston Med and Surg Jour, 1916, **175**, 191

23 Staubli Trichiniasis, J. F. Bergman, Wiesbaden, 1909

24 Schlecht, Heinrich Arch f exper Path u Pharmacol, 1912, **67**, 137

25 Staubli, Carl Ergebnisse der Inn Med v Kinderheilkunde, 1910, **6**, 193

26 Proscher Folia Haemat, 1905, **2**, 543

27 Schlecht, Heinrich Deutsch Arch f inn Med, 1912, **98**, 327

philia at the point of reinjection, and later a general increase in the number of these cells (Schlecht and Schwenker²⁸)

On account of these many past observations, it was anticipated that the finding of an eosinophilia might indicate an extrinsic cause of asthma, and also that it might indicate resistance to the foreign protein responsible. As will be shown in the following, these hypotheses have not been substantiated by the present work.

(3) *On Treatment*—This latter point needs further comment. It is known that ordinary hay fever can be much alleviated by repeated parenteral injections of the particular pollen extract to which the patient is sensitive (Cooke,²⁹ Goodale,³⁰ and others). Horse asthma also can be successfully treated with horse hair protein (Goodale,³⁰ Cooke,³¹ Walker³²), and Schloss⁴ treated his egg sensitive baby with small and repeated doses of egg-white.

Having made a tentative diagnosis of the kind of asthma in these patients, a good check on this diagnosis has been the result of specific treatment. Thus, treatment often has a bearing on the diagnosis.

The treatment of asthma by repeated injections of the patient's own blood defibrinated, was suggested by Kahn and Emsheimer³³. It has been tried in three patients but with no permanent result.

The groups under the division of extrinsic asthma include pollen asthma, horse asthma and acute food asthma.

POLLEN ASTHMA

Twenty-four cases gave a definite history of aggravation of asthma during the summer months, and all but five gave a positive skin test to extracts of one or more pollens. They are, therefore, grouped together. It seems reasonable to assume that these individuals are all susceptible to plant pollen. This susceptibility is a highly specific one. The onset date of the autumn asthma is, in several histories, almost exactly coincident with the onset date of many cases of simple uncomplicated hay fever, and in about half of twenty-four cases the asthma ceases abruptly with the first frost. On these accounts, we may say that anaphylaxis in the strict sense plays an important part in these cases and that in twelve of them it is the only factor.

28 Schlecht and Schwenker. *Deutsch Arch f klin Med*, 1912, **108**, 405

29 Cooke, R. A. *Treatment of Hay Fever*, Laryngoscope, 1915

30 Goodale, J. L. *Vasomotor Disturbances of the Upper Air Passages*, Boston Med and Surg Jour, 1916, **175**, 181

31 Cooke, R. A. *Personal Communication*

32 Walker, I. C. *Jour Med Research*, 1917, **35**, 497

33 Kahn and Emsheimer. *THE ARCHIVES INT MED*, 1916, **18**, 445

However, in the other twelve there must be another factor, because these twelve cases have asthma at other times as well, the cause of which is in most cases a mystery

The five patients who failed to give a positive skin test to one or more of the pollens are detailed in the following reports (refer to Table 1)

TABLE 1—POLLEN ASTHMA TWENTY-FOUR CASES

Case No	Sex*	Present Age	Age at Onset	Hay Fever	Skin Tests to Pollens	Asthma Worse in Summer	Asthma at Other Times	Treatment With Pollen Extracts	Family History	Eosinophilia, per Cent	
										In Attacks	Between Attacks
8	♂	22	5	+	+	+	0	++	+		
16	♂	26	24	+	+	+	0		0		
21	♀	6	4	0	+	+	0		+	0	56
32	♀	48	30	+	+	+	0	++	+		16
36	♂	12	6	0	0	+	0		0		
53	♀	38	34	+	+	+	0		0		2
62	♀	11	9	0	+	+	0		0	12	5
106	♂	46	31	+	+	+	0	+++			03, 03
116	♂	31	21	+	+	+	0	++	+		
126	♀	28	28	0	+	+	0			2	
135	♂	54	37	0	0	+	0				
143	♂	3	1	+	+	+	0		+		
2	♀	23	19	+	0	+	+	0	+	93, 93	26
3	♀	51	50	+	0	+	+		0	4	10
10	♂	55	53	+	+	+	+				2
12	♀	43	39	+	+	+	+		+	46	83
14	♂	13	8	0	+	+	+			10	5
49	♂	35	30	+	+	+	+	±	0	3, 26	
77	♀	44	30	+	0	+	+		+		
105	♀	25	16	+	+	+	+		0		3
110	♂	39	31	+	+	+	+			53	
112	♀	52	21	+	+	+	+	+	+	0	66
121	♀	36	26	0	+	+	+		0	4, 5	10
155	♂	50	39	0	+	+	+		0		26

* ♂ = male, ♀ = female

SUMMARY OF CASES

CASE 77—This case is interesting because, although the patient gave no skin tests, she had a typical hay fever from July until frost, a positive family history, and during this hay fever often had urticaria

CASE 135—This patient is a hostler, aged 54, with asthma for seventeen years which comes on only in the autumn, usually late in August. In spite of a negative test to ragweed and no hay fever he is grouped here. He might very possibly give a test with some other of the compositae

CASE 36—A boy, aged 12, had asthma only during the summer. In spite of the fact that chest roentgenograms showed the presence of a large mediastinal gland, in spite of the negative skin tests and the absence of any history of hay fever, he is inserted in this group because in the winter he is perfectly well.

CASE 10—Although this patient had had hay fever from August until frost for thirty years (since the age of about 20), it was only during the past two autumns that he has had asthma coming at the same time with the hay fever. However, during the past two winters he has had recurrences of asthma probably dependent on a chronic bronchial infection.

CASE 3—This patient failed to give a positive skin test to any of seven different pollen extracts. She was susceptible to roses and her asthmatic attacks most commonly began in the mountains of New Hampshire in the summer, and were much worse during her three weeks' stay there. She has also had slight asthma at other times.

Treatment consisting of hypodermic injections of ragweed pollen has been carried out in only seven of these patients (Cases 2, 8, 32, 49, 106, 112 and 116), but it gave definite relief in five, and one case was practically entirely relieved.

CASE 2—(Illustrates the importance of the skin test.) A girl, aged 23, had asthma for three years, much worse during June and August, but also at times during the winter. She also had hay fever and on this account was treated with ragweed pollen extract in spite of the negative skin test, but with almost no benefit. It is interesting to note in passing that she has *not* developed a positive skin test as a result of the treatment.

Twelve cases not classed as pollen asthma (Cases 5, 11, 15, 20, 35, 48, 80, 119, 123, 133, 144 and 150) gave a positive skin test to ragweed pollen. They are of special interest since none of them had hay fever nor increase of their asthma during the ragweed season. These cases show the necessity of agreement between skin test and history in order to prove the etiologic part played by pollen. It would be interesting to treat some of these cases to emphasize this point.

CASE 67—(Closely related to this group.) A woman, aged 31, had asthma for two years and also had definite hay fever together with a positive skin test to ragweed pollen. She cannot be included in this group, because her asthma was not aggravated while the hay fever was in progress.

HORSE ASTHMA

Before taking up the clinical aspect of horse asthma, it is important to emphasize the observations of Walker,³² Goodale,³⁰ Cooke,²⁹ and others on the definite anaphylactic specificity of horse hair protein and of horse serum.

As will be brought out in the following pages, thirty-seven patients gave a positive skin test to horse hair extract, whereas only six of these individuals gave a positive skin test to horse serum as well.

To test further the specificity of these two substances an attempt was made to sensitize guinea-pigs with one substance and shock them

with the other, but without positive results, as shown in Table 2. The horse hair extract used was the same extract used for the skin tests and contained in this test 2 mg of nitrogen per cubic centimeter (100 times as much nitrogen per cubic centimeter as is used for skin tests).

This experiment shows the absence of any protein group-complex such as Wells³⁴ describes as theoretically responsible for some of the crossed anaphylactic reactions with various vegetable proteins, which might be common to horse serum and horse hair extract.

TABLE 2—ANAPHYLACTIC REACTIONS OF HORSE SERUM
AND HORSE HAIR EXTRACT

Guinea Pig No	First Dose Intraperitoneal	Time Interval	Second Dose Intravenous	Result
1	1 c c horse hair extract	24 days	0.4 c c horse serum	No symptoms
2	1 c c horse hair extract	24 days	1 c c horse hair extract	Dead in 2 minutes
3	0.2 c c horse serum	24 days	1 c c horse hair extract	No symptoms
4	0.2 c c horse serum	24 days	0.5 c c horse serum	Dead in 2 minutes

Of the thirty-seven patients with positive tests to horse hair extract, sixteen were considered to have horse asthma. Thirteen of these gave a definite history of attacks occurring soon after coming near or remaining in contact with horses. All thirteen gave a markedly positive skin test to horse hair extract. For example:

CASE 34—A fireman was much affected by asthma until the former horse engine was replaced by a motor vehicle, whereupon his asthma definitely improved. Since that time, he occasionally is required to substitute at a station where they have horses and it is very instructive to learn that he becomes wheezy after being in this station *for twelve hours*, and again that this wheezing persists for about eighteen hours after he leaves the station.

This is a different story from that of the following patient:

CASE 113—A girl, aged 22, although brought up among horses in Texas, taking the full care of them and riding a great deal, had no trouble until after the age of 14. Ever since then, whenever she rides horseback, running of the nose, smarting and burning in the eyes begin in *a matter of minutes* and if the ride is a long one, definite asthma comes on and persists for an hour or two after the ride is over.

The time relations in these two cases are especially interesting and instructive. Do they show more than different degrees of sensitiveness?

34 Wells, H. G., and Osborne, T. B. Biologic Reactions of the Vegetable Proteins, *Jour Infect Dis*, 1913, **12**, 341.

Three other patients who gave a positive skin test to horse hair gave also a history of asthma in attacks which were associated with different places and circumstances at least compatible with exposure to horses or other animals or to horse dust

CASE 146—A girl, aged 9, whose attacks came every other week, lasting one week, and who drove to school each day behind a horse

CASE 61—Who had asthma when living on a farm in winter

CASE 58—A girl, aged 10, who had asthma once a week which was definitely worse when the east wind blew toward her house from a stable across the way The girl was somewhat improved on treatment with horse hair extract

TABLE 3—HORSE ASTHMA SIXTEEN CASES

Case No	Sex*	Present Age	Age at Onset	History	Skin Test to Horse Hair	Skin Test to Horse Serum	Skin Test to Dog Hair	Other Skin Tests	Results of Treatment With Horse Hair Extract	Family History	Eosinophilia, per Cent	
											In Attacks	Between Attacks
4	♂	13	10	+	+	+		Rag gold, aster Sera (R=0) Rag		+		13 3
13	♂	38	8	+	+	+	+		+	+	2	2 3
9	♀	31	3	+	+	0				+		
34	♂	25	22	+	+	0				0		11, 4
45	♂	60	2	+	+	0		0		+	5 3	
58	♀	10	4	±	+	+		0		+		4 3
61	♀	40	34	±	+	0				0		5
103	♀	33	18	+	+	+	+		++	+	8	3, 5 3
113	♀	22	14	+	+	0	+		++	0		2 6
115	♀	45	21	+	+	0		Rag	+	+	7 6, 4	
131	♀	23	18	+	+	0		Rag, grass? 0		+	11	
132	♂	29	26	+	+	0		0				4 6
140	♀	17	15	+	+	+		Rag		+		9
141	♀	48	28	+	+	0		Rag, grass, red top	+++	0	3 6	7 3
146	♀	9½	7	±	+	±	+			0	7	
157	♂	23	1	+	+	+		Rag		+		

* ♂ = male, ♀ = female

Of these sixteen patients, five have been under treatment with horse hair extracts, and all have been helped to a greater or lesser extent Two of these patients, Cases 13 and 103, however, were the subject of a paper entitled "Interesting Reactions Obtained During Treatment of Two Cases of Bronchial Asthma,"³⁵ in which rather alarming even though transient anaphylactic responses were described

³⁵ Rackemann, F M Interesting Reactions Obtained During Treatment of Two Cases of Bronchial Asthma, Jour Am Med Assn, 1917, **69**, 889

The other eleven have been told simply to avoid animals, and as a result most of them have remained comfortable Table 3 gives a general summary of the cases in this group

Besides these sixteen more or less clear cut cases of horse asthma, there are twenty-one cases who give a positive skin test to horse hair and yet do not give any history of horse susceptibility

Eight of these have already been included under pollen asthma They give skin tests to both ragweed and horse hair, but were classed as pollen cases because of the seasonal increase in their symptoms Five more (Cases 30, 48, 66, 80 and 119) are discussed under "Bronchitis," two under "Tuberculosis" (Cases 74 and 96), two under "Gastro-Intestinal Asthma" (Cases 38 and 118), and four others are still unclassified (Cases 17, 63, 127 and 136) Two of these last are worthy of special mention

CASE 63—A woman, aged 21, has had asthma every one to four weeks since infancy These attacks come on at all seasons of the year She repeatedly gave a positive skin test to horse hair extract She has been followed for nearly a year When first seen she cleared up rather promptly on five doses of the extract and then remained well for about three months (two months after the end of the treatment) She has asthma at the seashore, it came on again soon after her arrival, thus ending the three months period of freedom, and the asthma returned part of every week all summer In the autumn, injections of horse hair extract were begun again, the improvement was not as marked as before, but she felt much relieved after each dose, so that now she returns to the hospital for treatment whenever she feels another attack is pending She gives no history of being sensitive to horses Her attacks are in no way associated with them and yet the injection of extract seems to have a definite effect In this way, she seems to be an exception to the doctrine of the necessary positive history

CASE 136—A man, aged 22, gave an intense reaction to horse hair extract and also to ragweed He had typical hay fever from early August until frost for four years, and in the past four years had asthma But this asthma comes on at any time of year, often when snow is on the ground and is, therefore, not a true pollen asthma No focus of infection was found after careful search, and his family history was negative His eosinophils were 6 per cent In view of the skin test, he was given repeated doses of horse hair extract, but with no result whatever He repeats the assertion that he is not affected by horses and can go into a stable without difficulty, so that this positive skin test becomes merely an observation, the significance of which is as yet unknown

Why these twenty-one cases should give a positive skin test to horse hair is quite unknown Many of them gave the test with more than one extract of horse hair showing the probability of the reaction being really a specific one

The results of treatment in Case 63 are very interesting, and according to other experience in this work, are distinctly unusual

It should be emphasized again here that these horse hair extracts were tested on many more than twenty-one other patients who gave no reaction at all, so that the extract cannot be classed as an irritant per se

ACUTE FOOD ASTHMA

Only two cases in this entire group of 150 cases of asthma gave a history of exquisite susceptibility to food

In taking the histories of each of these 150 patients, special attention has been paid to the question of food poisoning. This attention was, to a large extent, because of the recent interest in the possible relation of the ingestion of many different foods to not only asthma in particular, but anaphylactic states in general. Furthermore, many of these patients have been treated by omitting various biologic groups of food in rotation but never with beneficial result.

CASE 41—A medical student, aged 24, whenever he eats fish or shellfish of any kind has, within a few minutes, swelling of his lips and tongue which develops into a general urticaria and within from ten to fifteen minutes leads to sneezing and asthma. Skin test to fish extract is intensely positive. His sister has hay fever, his mother has gastro-intestinal upsets, nausea, vomiting and diarrhea from eating fish. It is interesting to note that he has no marked eosinophilia. Counts made on two occasions gave figures of only 46 per cent and 23 per cent, respectively. He knows his trouble well and remains in every way in perfect health as long as he avoids fish.

CASE 117—This case is less striking. A girl, aged 3 years, at the age of 9 months developed eczema and urticaria in attacks. It was later discovered that ingestion of eggs caused immediate vomiting and swelling of the mouth and some slight difficulty in breathing. This child gave a markedly positive skin test to a solution of egg-white. The father has urticaria after eating strawberries, the mother had an attack of urticaria seventeen years ago, cause unknown. As far as is known, this child did not receive any egg until the age of 2. Since the test, egg has been excluded from the diet, but the eczema still persists so that its cause is not yet known. Skin tests to animal serums and hairs, to ragweed pollen, to fish extract and to milk, were all negative.

With these two cases, the extrinsic causes of asthma as found in this study have been covered. A total of forty-two cases, or only 28 per cent of the whole number.

Intrinsic causes of asthma acting from within the body, as opposed to extrinsic causes—acting on the body from without, are now to be discussed.

GASTRO-INTESTINAL

In five patients, derangements of the gastro-intestinal tract seem to be a possible cause of their asthma.

CASE 38—This patient had asthma for fifty-two years and maintains that any rich food which causes indigestion will precipitate an attack. He gives a positive skin test to horse hair and ragweed. He had "hay fever" all the year round up to ten years ago, which stopped with an operation on his nose, but asthma still continues.

CASE 122—There is a history suggesting peptic ulcer and roentgenograms revealed a small ulcer in the region of the pylorus. Although he had a very light attack of difficult breathing nine years ago, he was free of asthma until about the time that his stomach began to trouble him. He also had an

emphysematous chest Skin tests, family history, eosinophil counts and the search for various foci of infection were all negative A five-meal diet with occasional doses of soda have relieved him, but he still has asthma

CASES 52 AND 159—These patients, aged 8 and 12, respectively, were relieved when meat was reduced in their diet

CASE 118—This patient has been studied carefully A man, aged 30, has had asthma in weekly attacks for two years There is no evidence of anaphylaxis except for an unexplained skin test to horse hair There was no family history and no eosinophilia Change of residence has not helped his asthma Treatment of obstinate constipation relieved his asthma markedly when first seen, so that he had no bad attacks for two months, but he relapsed again A second examination by the roentgen rays revealed a definite abscess at the roots of two teeth, a normal gastro-intestinal tract, normal nasal sinuses, but in the roentgenogram of the chest, there was a mottling along the markings, especially those running to the apices and shadow of the hylus which was unusually large

Perhaps a tuberculosis of his bronchial glands was the true diagnosis, but if so, why the attacks and especially the two months period of freedom?

The possibility that, in some cases, disturbances of the metabolism of one of the three great classes of food might be at fault, must be considered When, for example, asthma may be due, not to one particular protein, but to proteins, or, perhaps, carbohydrates or fats in general, as a class Examination of the stools might be a distinct help in these conditions

ACUTE BRONCHITIS

Twenty-four cases of bronchial asthma have attacks in which a cough is a prominent symptom, which attacks come on at fairly long intervals, usually several weeks, and have absolutely no relation to season, locality, weather, or dietary indiscretion, although the attack usually begins with a "cold"

Physical examination of these patients shows during the attack, the lungs full of sibilant and sonorous râles, but there is little change in the character of the breathing Usually there are a few fine moist râles present in the bases No other pathologic change has been made out, nothing appears on special examination of the nose and throat, and a roentgenogram of the chest reveals at the most a "thickening of the lung markings" There is little or no fever during the attack

Between attacks these patients are quite normal, and providing they avoid taking cold again and avoid undue exertion or exposure such as swimming in cold water, can do or eat almost anything without return of their symptoms

As will be seen by the accompanying table (Table 4), out of twenty-four patients presenting this clinical picture, seven gave a skin test to ragweed and four to horse hair as well, and one to horse hair alone Five were not tested at all Explanation of these positive tests

TABLE 4—ACUTE BRONCHITIS TWENTY-FOUR CASES

Case No	Sex*	Present Age	Age at Onset	Interval of Attacks (Weeks)	Duration of Attacks (Days)	Skin Test	Other Anaphylactic Reaction	Food	History of Attacks Associated With	Family History	Eosinophils, per Cent	
											In Attacks	Between Attacks
18	♀	30	25	4-24	3-4 14-21	0	0	Teeth	"A cold" winter or summer	0		16
24	♀	23	1½	8-12	4-42 av 7	0	0		Outmenia	0		
30	♀	41	17	8-250 av 12	3-4	Rag ? H H ?	0		"A cold" (has nephritis)	0		
31	♀	52	5	24	3-4	0	0	0	"A cold"	0		
33	♂	47	40	24	3	0	0	T B ? teeth	Spring and fall, worse lately	0		26
35	♂	9	1	6-24	1-7	Rag, clover	0	0	"A cold" winter or summer (old empyema)	0		
37	♀	22	31	4-12	1-5 lately steady	0	0	T B	"A cold"	0	11 21	113
40	♀	35	33	2-24	7-11 -120	0	Hay fever	Teeth	Last wind, cold and damp weather	0	6 43	
42	♀	50	27	12-24	2-7	0	0	(?)	Abdominal pain, indigestion	+	1	
48	♂	31	29	1	1	Rag, H H R T	0	0	Weather changes	0		
51	♂	34	34	12	2-14	0	0	Teeth	"A cold"	0		
54	♂	7	5	8-12	4-5	0	0	Possibly posture	Suggests early tuberculosis (?)	0		
56	♀	10	5	1-12	1-2		0	Teeth	"A cold"	0	11	
57	♂	9	7	24	2-7 -75		0	Teeth	"A cold"	+	133 7	
60	♂	25	8	20	1-12	H H	0	Teeth	Spring and fall			16
80	♂	34	21	2-3	1-3	Rag H H	0		"A cold", recent pneumonia	0		0
61	♂	19	18	24	3-4		0	0	(?)	0		
93	♀	17	9	2-4	1-2		0	Posture	(?)	0		
101	♀	40	35	1-8	7-14	Rag	0	Teeth, constipation	(?)	0		16
110	♂	38	30	1-8	2-6 hrs	Rag H H H S	0	0	(?)	+		53
125	♀	43	15	52 April	2-3 -60	Rag	0	0	(?)	0	13 123	
131	♂	22	14	8	4-5		0	Septum	"A cold"	0		
145	♂	9½	9	1-8	7	0	0	Teeth	"A cold"	0		66
149	♂	26	18	24	3-14 -60	0	0	0	"A cold"	0		

* ♂ = male ♀ = female

is difficult Suffice it to say that none of these patients had hay fever nor were any of them susceptible to horses as such, and furthermore their attacks came at irregular and odd intervals

Only three patients had a positive family history

Five of these patients (Cases 48, 93, 101, 119 and 145) differ from the others, because of the relatively short intervals between their attacks, but except for one (Case 48) the other four often went at least from one to two months without an attack

It will be observed that the duration of attacks was in only eight patients (Cases 18, 24, 37, 40, 57, 66, 125 and 149) ordinarily more than fourteen days, and of these eight, in at least four (Cases 37, 57, 125 and 149), it is only recently that the character of the attacks has changed from their former and original short duration

In regard to the histories Asthma was associated with "a cold" in twelve patients with changes in weather, especially in the spring and autumn in three, often with catamenia in one, with indigestion in one, and with unknown circumstances in six

It is of importance to note that only one of these patients (Case 40) gave any history of hay fever, she gave no positive skin test and had this hay fever during only a period of five years ending four years ago

Except for this one instance, there was no other evidence of any other anaphylactic manifestations, such as hay fever, hives or food poisoning in this group

Since these twenty-four patients have attacks at such irregular intervals which do not correspond to any season, place, or circumstance, and since their skin tests seem to be, as far as we have gone, merely isolated observations it seems reasonable to assume that these patients suffer from the effects of something that they carry about with them, that their asthma is dependent on an intrinsic and not extrinsic cause The theory that this intrinsic cause is a bronchitic infection is, of course, only a tentative explanation based on no definite grounds except the predominant cough and increase of expectoration, but, on the other hand, recurrent attacks of bronchitis are at least more common, in general, than similar recurrences of many other infections

In the column headed "Foci" (Table 4) it will be seen that thirteen patients had a recognizable focus of infection It does not seem likely that bad teeth, for example, could cause attacks of asthma at from 2 to 6 months intervals True, the effect of extracting these teeth has, in most of these cases, not been studied Two patients (Cases 33 and 37) showed signs at the lung apices suggesting tuberculosis, but it was finally agreed that these signs were not definite enough to warrant the diagnosis

WINTER ASTHMA

In Osler's "Practice of Medicine," 1909, page 633, a description is given of emphysema which exactly fits a certain group of cases referred for "asthma." Little is known of the etiology of this group of cases, and they have been studied here, in the first place, to discover any possible etiologic relation to proteins, and in the second place, to see if they had anything in common, except difficulty in breathing, with other and more clear cut cases of asthma.

A brief description of these cases is a necessary repetition in order to define the object of study.

There is a group composed for the most part of older individuals whose asthma overtakes them with the onset of cold weather and they remain wheezy and short of breath, especially at night, until summer.

These cases give no skin tests to those foreign proteins of animal or vegetable origin which were tried. Their asthma is often severe and they can do little but sit quietly and try to breathe.

They present on examination very commonly a barrel chest, which is everywhere hyper-resonant so that the true heart borders are often obscured. They all have a peculiar "asthmatic" or nasal quality to their voice, a sign which is easily recognized, and often characteristic. Many of them raise considerable quantities of a white frothy sputum which usually contains numbers of eosinophilic leukocytes. At times the sputum is purulent and then contains a varied assortment of organisms in considerable quantities.

Asthma in these individuals is very much worse with any exertion, and if they can remain for a time quiet and especially in a warm atmosphere, their symptoms abate promptly.

Examination of the heart, determination of the blood pressure and examination of the urine have failed to reveal any important circulatory lesion in these cases. Most of them have emphysema and chronic bronchitis. In these patients potassium iodid usually gives great relief.

There are two fairly distinct groups of patients to whom the above description applies. They have been separated in this work, because while one group seemed to have asthma only in the winter and are quite normal in summer and warm weather, the other group has asthma off and on more or less continually throughout the twelve months. The first group has been styled "winter asthma" and includes here twelve cases.

As is shown on Table 5, five of these patients had asthma in very slight degree also at other times, but in the other seven, the asthma seemed limited to the cold weather. Eight out of the twelve had had bad teeth or trouble in the nose, one (Case 78) had her teeth extracted,

and another (Case 48) had her nasal polypi removed, but in neither case was there any permanent beneficial result to the asthma

It will be observed that the age of onset in only two patients was below 25, and that the average for the whole group was 43.2 years — there being three patients whose asthma did not begin until after the age of 60. Skin tests were not done in five because these patients gave no history whatever which might suggest any extrinsic cause of their asthma. Those skin tests which were done were all negative in all patients.

TABLE 5—WINTER ASTHMA TWELVE CASES

Case No	Sex*	Present Age	Age at Onset	Other Anaphylactic Reaction	Skin Tests	At Other Seasons	Food	Family History	Eosinophilia, per Cent	
									In Attacks	Between Attacks
6	♂	43	25	0	0	0	Eczema			
22	♂	74	70	0	0	±	0	0		
25	♂	64	62	0	0	±	Teeth	0	0, 1	
48	♀	40	38	0		0	Polypi			23
65	♂	43	38	0	0	±	Nose, teeth	0	13	
78	♀	44	32	0	0	0	Teeth out	0	11.4	53
99	♂	36	34	0	0	±	Teeth	0		
100	♂	61	46	0		0	0	0		
102	♂	36	32	0		0	Teeth, constipation	0		
104	♂	47	47	0		0	Teeth	0		23
107	♀	36	24	0		0	Teeth			
148	♀	74	70	0	0	±	0	0	4	

* ♂ = male, ♀ = female

Three patients (Cases 22, 25 and 148) should be really in a subgroup by themselves. In no one of them did asthma begin until after the age of 62. All three were elderly, tall, emaciated men with marked arteriosclerosis, with low blood pressure, clear, low gravity urines and regular pulses. All three were barrel chested with lungs full of squeaky râles, the breathing rather high pitched, prolonged and rather diminished in intensity. All three were slightly cyanotic. All three were helped to some extent by dram doses of a mixture of equal parts sodium bicarbonate and sodium phosphate which no doubt controlled the flatulency which, as Osler mentions, often accompanies emphysema. All three men were very uncomfortable, had to sit up in a chair practically all the time in winter, and often had to use most of the auxiliary muscles to breathe at all.

CHRONIC BRONCHITIS AND EMPHYSEMA

Except for the seasonal aggravation of their symptoms, these cases of winter asthma are in no way different from another group of cases which also have a chronic bronchitis as a basis for their asthma

TABLE 6—EMPHYSEMA AND CHRONIC BRONCHITIS EIGHTEEN CASES

Case No	Sex*	Present Age	Age at Onset	Other Anaphylactic Reaction	Skin Test	Foci	Lungs	Character of Attacks	Family History	Eosinophilia, per Cent	
										In Attacks	Between Attacks
7	♂	46	45	0	0			Steady	0	12	
19	♀	28	10	0			Bronchiectasis	Predominant cough		13	
28	♀	48	46	0	0		Ch Br	Steady	0	23	
43	♂	50	45	0	0		(Vaccines)	Steady for two years	0	0	
44	♂	48	48	0	0	0	Ch Br	Dyspnea on exertion	0	13 12.6 10.3	
47	♀	52	51	0	0	0		Attacks at all seasons, steady	0	5	
64	♂	39	31	0	0	Nose		Steady	0	3	
76	♂	33	31	0	0	Teeth antra		Cough for two years, dyspnea on exertion	0		
85	♂	17	3	0	H H		Ch Br	Growing worse, almost steady	0	3 1	
92	♂	48	41	0	0	Teeth	Ch Br	Worse in cold weather and on exertion		16	
94	♂	43	38	Hay fever	0	Teeth		Steady, but worse on damp days	0		13
97	♂	34	30	Urticaria	Rag	Antra (vaccines)		Constant wheeze, frequent cough, periodic attacks	0	3 3 5	
108	♂	45	30	0	0	Teeth	Ch Br	Steady	0		
111	♂	43	28	0	Rag H H		Ch Br	23 attacks a month lasting 2-3 days, weak spells, dyspnea on exertion	0	0 0	
154	♀	47	37	0	0	0	Heart?	Precordial pains, weak spells, dysp	0		14 10 9
20	♀	31	16	0	Rag	0	Br Glands, emphys	Steady		43 13	
82	♀	54	44	0	0	Polyp removed 3 times		Steady, every day for ten years	0		
160	♂	63	60	0		Teeth	Old tuberc	Steady	0		

* ♂ = male ♀ = female

This latter group includes eighteen cases who have asthma practically steadily without much relation to season (Table 6) They too have emphysema and suffer often intensely from shortness of breath

A careful history together with a careful examination fails to reveal any cause of asthma in these patients except the lung condition. Skin tests are nearly always negative. One patient had hay fever but the degree of asthma bore no relation to this and the hay fever had existed some years before the asthma appeared. Case 97 had urticaria (as described in the following pages). Aside from this, there was no history of susceptibility to proteins in the group.

CASE 64—This is a typical example. An Italian, aged 39, has had asthma for eight years practically every day. The asthma may stop suddenly in the middle of the day for an hour or so and then "he feels as good as any man." He was in the hospital ward for three weeks with little or no change in his condition and then his nose was operated on. Following a day or two of intense asthma, he began to improve somewhat, and though now some months afterward he still has asthma, he declares that he is "three times better than before."

CASE 97—This patient is interesting as showing the difficulties of treatment in these cases. He had bronchitis three years ago, which lasted two weeks and left him well, but eight months after this at the age of 30, he began to be wheezy and dyspneic. Since then he has had attacks every week or so which come on after eating or after exertion and last from one-half to three days. Except for one attack of urticaria four months ago, for which he can assign no cause, he has had no other manifestation of anaphylaxis. His eosinophils were never above 5 per cent.

Recently he has been observed on two occasions, two months apart, with a fever of 101 F, for which no cause has been found, but which came down after administration of salicylates. With this fever there was no special change in the asthma. His lungs show peculiarly loud wheezes throughout, which seem out of proportion to the degree of dyspnea. The roentgenogram suggests a diffuse bronchitis, no local focus was ever found in the lungs. Outside the hospital he has been given stock streptococcus vaccines, and these proving of no avail, he obtained an autogenous streptococcus vaccine from his sputum, doses of which were given every other day. As the doses were increased, he began to wheeze again and finally had a violent attack of asthma. His right antrum was cloudy and a roentgenogram revealed a possible infected root of a tooth, but neither of these foci was considered definite enough to warrant radical procedures. Changes in diet, first omitting all bread and all cereals for two months, and later omitting all meats, have given no results. Potassium iodid helps somewhat. Luckily his asthma is relatively mild.

CASE 85—This case is also typical of this group. The patient's history is given here in detail because of the very early age of onset.

A boy with asthma since the age of 3, but without any definite lesion to account for it. In the hospital he spent most of his time sitting on the edge of his bed breathing with difficulty—improvement was very slow. Inasmuch as there was nothing to go with it, the positive skin test to horse hair extract which was not marked was neglected. He had a typical emphysematous chest.

Two cases in this group show an eosinophilia.

CASE 154—This patient's history of precordial pains, and weak spells followed by dyspnea is not usual in asthma. Her chest was thick, hyper-resonant and there was prolonged expiration, she had an eosinophilia of 10 per cent which so far is unexplained.

CASE 44—This patient also had a barrel-shaped chest with prolonged expiration. He had no hay fever or other obvious protein susceptibility. He had had symptoms for only a year and yet three blood smears taken on dif-

ferent occasions in a period of three months while his lungs were full of râles showed an eosinophilia of 13, 12 and 10 per cent, respectively

The stools in both these patients were examined for parasites with negative results

CASE 160—This man, aged 63, has had asthma for only three years, and is another typical example of this group. He is of especial interest since he had tuberculosis fourteen years ago, with positive sputum and a tubercular laryngitis. At that time he was treated at the Rutland Sanatorium and in Colorado for two years and now presents only a healed process at the right apex. He had no asthma with this old tuberculosis.

A word should be said of the following case

CASE 19—A woman, aged 28, has had asthma since the age of 10, but in her case a cough was distinctly a prominent, if not predominant, feature. She raised considerable quantities of a greenish-yellow sputum, and roentgenogram revealed conditions quite typical of bronchiectasis.

Why should this woman among so many other cases of bronchiectasis have had attacks of shortness of breath?

It will be seen from Table 6 that two of these patients (Cases 64 and 82), with presumable lesions in the nose, had been operated on but without result.

TUBERCULOSIS

The association of asthma and tuberculosis has been discussed by O. Frankfurter³⁶ in 1913, who concluded that there was some causal relationship between them and who claimed that a systematic and long enough continued treatment with tuberculin may cause a diminution or cessation of the attacks.

Frenquelli³⁷ likewise had excellent results with tuberculin in two cases who had signs suggesting latent tuberculosis.

Giffin³⁸ saw eighty-two cases of spasmodic asthma, three of which had positive evidence of tuberculosis. During the same period he saw 226 cases of tuberculosis.

In this report it has seemed justifiable to include six cases under the diagnosis of tuberculous asthma, as shown in Table 7. Except for the two cases detailed in the following, the onset of asthma in these cases was quite coincident with the onset of the tuberculosis and on this account may be tentatively assumed to be dependent on it.

CASE 74—A man, aged 59, has had asthma all his life with attacks spring and fall, but for the past two years has had it constantly, has lost 20 pounds in weight and although no tubercle bacilli could be found in his sputum, there were signs at both apices with a possible cavity in the left. The attacks

³⁶ Frankfurter, O. Asthma and Tuberculosis, *Wien klin Wchnschr*, 1913, 26, 961.

³⁷ Frenquelli, J. Tuberculous Asthma, Two Cases, *Semana Med*, Buenos Aires, 1916, 23, 583, Summarized in *Jour Am Med Assn*, 1916, 68, 1011.

³⁸ Giffin, H. Z. Asthma and Tuberculosis, *Am Jour Med Sc*, 1911, 142, 869.

up to two years ago were possibly due to pollen. Skin tests are suspicious and the patient stated that he had hay fever both spring and fall, for which he went up to Bethlehem, N H, for relief. His tuberculosis, therefore, may have been an additional disease and not the cause of his attacks of dyspnea.

CASE 96—This patient had a history of hay fever and stated that his asthma was worse on arrival in Nova Scotia late in August, and lasted throughout his stay. He was in the hospital ward in February, had a continuous fever and showed signs of consolidation in his lungs. He died in April presumably of tuberculosis, although no necropsy report is available. The late onset of his asthma (age 42) argues against a simple pollen asthma.

TABLE 7—TUBERCULOSIS SIX CASES

Case No	Sex*	Present Age	Age at Onset	Evidence of Tuberculosis	Sputum	Sinus torium Treatment	Other Anaphylactic Reaction	Skin Tests	Family History	Eosinophils, per Cent	
										In Attacks	Between Attacks
74	♂	59	5	Lung sign	0	0	Hay fever	Rag H H	0	46	
83	♂	32	19	Hemoptysis, lung sign	0	Rutland 13 years ago	0		0		
87	♂	37	27	Lung sign	+	Rutland 10 years ago	0	0	0	26	
90	♂	20	20	Lung signs, fever friction rub	0	Rutland	0		0	10/8	
96	♂	45	42	Lung sign, irregular fever			Hay fever	H H	+		
124	♀	26	26	Hemoptysis lung sign	0	0	Hay fever				

* ♂ = male ♀ = female

Attention is also called to the following case

CASE 160—This patient (described under emphysema), had a positive tuberculosis, pulmonary and laryngeal, fourteen years ago, but *no asthma*, and now comes back with asthma dependent on emphysema and a chronic bronchitis, and presents no evidence of any active tuberculosis, although the right apex distinctly shows the old healed process.

NOSE AND TEETH

Four patients had lesions in the nose which were operated on, and to date the asthma in these patients has been helped (Table 8)

CASE 91—This patient had very bad teeth, one of which had a pus pocket which was probably connected with the antrum, as removal of this tooth showed a long dirty root.

CASES 142 AND 158—Both of these patients have emphysema. The former (Case 142) is interesting. Formerly his asthma came only in the summer, he had hay fever and today gives the corresponding skin tests. Now, however, his asthma has been steady until a marked improvement followed the nasal operation.

The latter (Case 158) was somewhat better after his operation but injections of a vaccine made from streptococci obtained from his antrum appear to have hastened this improvement markedly

Throughout this communication references have been made to the nose and teeth as a cause of asthma. These four cases are the only ones in which the possibility of such an etiology as a very important factor, becomes a probability. It will be remembered that Walker³ does *not* advise treatment of the nose, throat or teeth as a part of the treatment of asthma.

TABLE 8—NOSE AND TEETH FOUR CASES

Case No	Sex*	Present Age	Age at Onset	Interval Between Attacks	Duration of Attacks	Other Anaphylactic Reaction	Skin Tests	Bad Teeth	Nose	Treatment	Family History	Eosinophilia, per Cent	
												In Attacks	Between Attacks
91	♂	46	43	2-21 days	7-10 days	0	0	+	Antrum	Operd, slight result	0		
133	♂	28	5	1-7 days	1-2 days	0	0	0	Polyp	Tr. ben-zoin	0	9	
142	♂	60	10	†	†	0	Rag grass	0	Polyp	Regular treat		1 3	
155	♂	43	42	Steady	4 mos	0	0	0	Antrum vaccines	Operd, no result	+	7	8 13

* ♂ = male, ♀ = female

† Formerly only in summer, lately all the time

MISCELLANEOUS

Under this head various other intrinsic causes are grouped together

Bronchial Glands—Roentgenograms of the chest have shown shadows near the roots of the lungs in many of these cases. In five of these cases, however, sufficient emphasis has been laid on these shadows in the interpretation of the plates to warrant special attention here. One of these patients (Case 20) has emphysema, and is placed in that group. Another (Case 36) has asthma only in summer, and is grouped under pollen asthma. This leaves then only three patients in whom it seems reasonable to assume that enlarged bronchial glands may be responsible for the asthma.

CASE 89—A boy, aged 16, thin, pale, and thick-chested, gave a history of asthma almost daily since babyhood. Skin tests, eosinophil counts and family history were negative, but the roentgenogram revealed large mediastinal glands.

CASE 128—A leather worker, aged 30, had asthma steadily for fifteen years, for which no other cause could be found except "a large mass of thick glands in the region of the hilus of the lung." Skin tests were negative. His asthma bore no relation to reason, locality or occupation. There was, however, a two year period of freedom ending three years ago.

CASE 152—This patient had had a cervical adenitis, probably tubercular, which makes the diagnosis in her case all the more plausible.

It is important that these three patients had asthma which was steady without distinct remissions. The two years freedom from asthma in Case 128 cannot be explained.

This persistent character of the asthma would naturally be consistent with a more or less permanent obstruction to the flow of air in the larger bronchi, or with irritation of the autonomic nerve supply to the bronchial muscles.

Lordosis—One patient had this complication.

CASE 39—A stout Jewess, aged 42, has been relieved entirely of continued though mild asthma of four years' duration, by correcting a bad lordosis with a proper corset. Needless to say, her skin tests, family history, and eosinophil count were all negative.

Pregnancy—Two women had asthma definitely associated with pregnancy.

CASE 86—This patient had intense asthma throughout her third pregnancy which disappeared a month after forced delivery at eight months. There was no asthma with her two earlier pregnancies. After delivery she had a constant eosinophilia of over 10 per cent.

CASE 109—Asthma occurred with her first and second pregnancies, seven and one year ago, respectively, but since then she has had asthma with changes of weather so that, recently at least, it may be due to some infection.

Catamenia—In two other patients asthma was clearly associated with the catamenia.

CASE 88—She had attacks every four weeks for about five years.

CASE 153—This patient also had attacks closely associated with the catamenia, but these occasionally came at other times as after exposure, exertion, etc.

Circulatory—In only two cases, could asthma be definitely ascribed to circulatory disturbances.

CASE 129—A woman, aged 50, had asthma for three years, acute attacks coming on from three to four times a year. Her heart was a trifle large, blood pressure, systolic 180, diastolic 100, and there were moist râles at the base of the lungs.

CASE 130—An obese Syrian woman, aged 29, had asthma for eight years with dyspnea on exertion between attacks, with edema of the ankles and some orthopnea. Little, however, was found on examination of the heart, blood pressure, or urine, to account for the trouble.

Even in these two cases the diagnosis of myocardial incompetency is, perhaps, open to doubt, and the asthma may well have been dependent on some other cause. As stated earlier, no cases with definite lesions readily demonstrable have been included in this report, consequently, cardiac asthma, as such, has not been considered.

UNCLASSIFIED

In this group are placed a number of cases, the causes of whose asthma are still unknown, either on account of as yet insufficient study or because a careful study has failed to disclose any etiologic factor which seemed to be reasonable. Included here are fourteen cases which have already been discussed in connection with other groups, but have been finally found not to belong in those groups. This brings out the fact that in many cases the history and findings conflict in such a way as to leave the diagnosis much in doubt.

CASE 67—This patient is discussed under pollen asthma.

CASES 63 AND 136—Both are discussed under horse asthma.

CASES 73 AND 79—In these cases no cause could be found. They had negative skin tests, doubtful family histories, and one of whom had an eosinophilia. They gave positive Wassermann reactions. Antisyphilitic treatment has, however, not been carried out so that the diagnosis of syphilitic asthma is not yet confirmed.

Five patients (Cases 1, 70, 71, 98 and 151) discussed under nervous asthma, should also be listed here, because in no one of them is a definite cause of their asthma proved or disproved.

Case 84, discussed under the subject of the effect of ether, also belongs here, as well as three cases given as part of six cases with eczema. In addition to this total of fourteen cases, there are still fifteen cases which are all represented on the accompanying Table 9. Three of these seem of sufficient interest to be detailed here, and their histories follow.

CASE 5—A woman, aged 47, caught a cold eight years ago and had a mild attack of asthma for three weeks, this attack repeating itself every two or three months especially in winter, with comparative freedom between attacks. In the past three years, her asthma has been more or less constant and she has spent weeks at a time in bed, the same winter or summer. She gave a positive skin test to ragweed pollen but never had hay fever. She remained in the wards for two weeks and a half with asthma of severe type. Three days after an injection of 125 c.c. of her own defibrinated blood, she began to improve and with two other and larger doses, she left the hospital in ten days (November 19) with her lungs absolutely clear. She returned December 7, for 20 c.c. blood. December 13, she again had severe asthma. At her home, she was given 25 c.c. of her blood, which had absolutely no effect. On December 24, she struggled to the hospital, where the asthma continued unabated until January 11, during which time, she had five doses of her own blood. On this day, potassium iodid was given and she improved at once, and *has remained entirely well* for a period of eleven months. During her severe asthma, she had an eosinophilia of from 6 to 14 per cent which disappeared with her improvement. It is, perhaps, important to note that she also suffered from arthritis which seemed to alternate with her asthma.

CASE 114—A physician, aged 53, has had asthma since the age of 25. The attacks used to come on with his hay fever, but recently he has them constantly. A year ago he was in bed for six weeks with asthma. His pulse at that time

was intermittent and slow, but became very rapid on the least exertion. Lately, examination, even including roentgenograms of the chest, also an electrocardiogram, has failed to reveal any lesion. His breathing is not especially characteristic of emphysema. A lesion has lately been found in his nose, but has not yet been treated. Digitalis has not helped him.

TABLE 9—UNCLASSIFIED FOURTEEN CASES (ALL MENTIONED IN OTHER GROUPS)

Case No	Sex*	Present Age	Age at Onset	Other Anaphylactic Reaction	Skin Tests	Character of Asthma	Remarks	Family History	Eosinophil per Cent	
									In Attacks	Between Attacks
67	♀	31	28	Hay fever	H H Rag	Steady	"Pollen"	0	4, 1	
68	♀	21	1	0	H H	Every 14 weeks, $\frac{1}{2}$ 7 days	"Horse"		6	2,
136	♂	22	18	Hay fever	H H Rag	Slight attacks every 1-4 months, recently worse		0	48	
73	♀	42	40	0	0	Steady	"Positive Wassermann"		8	
79	♂	24	14	0	H H	One night a week 2 years steadily				
1	♂	11	9	0	0	Every 13 weeks, lasting 13 days	"Nervous"		12.5	
70	♀	49	41	0	H H Rag	Autumn for 5 yrs, steady for 3 yrs		0	1, 6, 1	
71	♂	29	22	0	0	Only in factory				
98	♂	21	6	0	H H Rag	State of Maine		0	1	
150	♀	10	9	0	H H Rag	Only in Lynn, not in Salem	(Eczema)	0		
84	♀	30	28	0	0	Attacks at long intervals	Ovarian cyst and teeth	0	15.6	
123	♂	14	3	0	Rag grass	Three days a week, same winter and summer	"Eczema"	0		
144	♂	7	7	0	Rag	Steady for 1 month	"Eczema"	0	8.5	
151	♂	46	40	0	0	On shore, not at sea				

* ♂ = male ♀ = female

CASE 156—This case is of special interest. A professional masseuse, aged 29, drives about in a Ford automobile. After cranking the car, she enters and drives for about a minute, when severe asthma comes on and continues for over half an hour. If the Ford starts very easily, she has no trouble. Indoors, she can run up three flights of stairs without trouble. Careful physical examination by a leading clinician, roentgenograms of the chest and teeth, skin tests, special examination of nose and throat, all have been negative. At one time tuberculosis was suspected. Recently she has improved on 5 grains of calcium lactate, three times a day. How much of her asthma is "nervous"?

VARIOUS OTHER RELATED TOPICS

In addition to this detailed discussion incidental to the grouping of the individual cases, there are several interesting topics which are more or less related to the whole subject of asthma. Some of these which have come out in the study of these 150 cases as a whole are discussed here.

NERVOUS ASTHMA

Out of the total of 150 cases, there seemed to be at least six, in which the nervous or psychic element seemed to play an important part. These cases have each been studied carefully, and distinct effort has been made to account for their asthma otherwise. They are of importance, because if the diagnosis is really correct, some light may be thrown on the entire subject. Their histories are, therefore, detailed here.

CASE 1—A boy, aged 11, had asthma for two years, his mother's mother is said to have had asthma. He had had asthma, coughing and dyspnea, every week or two for from one to three days at a stretch, with no relation to season or place. He remained in the hospital for two weeks, was up and about the ward, was eating a full house diet, and yet had absolutely no symptoms, all skin tests were repeatedly negative. The night after he went home he again had an attack. His home was investigated. The family had moved after his first year of asthma without result. Sleeping in different rooms, and on different beds and pillows, was of no avail.

He visited his father's mother, and was completely relieved as long as he stayed there. Her house was only a mile or two from his home, so that he attended the same school, and, as far as could be made out, ate the same sort of food. His teeth and throat were good. His posture was poor.

Was there something in his mother's house which caused his asthma, or was it dependent on a purely psychic disturbance, possibly due to his mother's overindulgence? Two findings are against the diagnosis of nervous asthma which otherwise seems necessary, the age of only 11, and the eosinophilia of 12 per cent.

CASE 150—The case is of very much the same type. A girl, aged 10, has had a cough and been short of breath at night for a year. She sleeps poorly, has enuresis and is constipated. She lives on a small truck farm where there are various animals and a small garden. As she gave a positive skin test to ragweed and to horse hair, her mother was advised to send the child to her grandmother's in the next town. A letter within three months afterward, states that the child is absolutely well and normal in every way. The asthma began two years before the family moved to the farm when they had no animals and no garden. The child was first seen late in October when true pollen asthma is over for the season.

CASE 70—A woman, aged 49, had asthma dating from her arrival in San Francisco from Australia, at the age of 32. Her father's father had asthma, and a brother has hay fever. She came straight to Massachusetts and was well for eight years, when, at the age of 41, she suddenly began to have hay fever in August. The next year again hay fever, and this time asthma with it, and this combination has recurred each fall. Three years ago the asthma became chronic, and was so steady and so severe that she took morphin, and at the time of her admission to the hospital on March 3, 1917, was taking about 1½ grains daily. She entered the ward an emaciated, rather excited,

apprehensive, restless little woman, showing marked pigmentation, probably due to morphin

She remained in the ward from March 3 until June 14, and throughout that long period she had to be given an average of about six doses of adrenalin chlorid in the twenty-four hours, to control her suffering

She gave definite skin tests to ragweed, to horse hair, and to horse serum, but no tests to grass pollen. Treatment with horse hair extract was attempted, but after no result from five doses was abandoned. She was given four doses of her own defibrinated blood, with no result. Atropin, nitroglycerin, amyl nitrite, asthma powder, oxygen to inhale, pituitary extract were all tried, but in vain. Transfer to a private room made no difference. Eosinophils were found in her sputum, but in her blood were never over 6 per cent.

Special examination of teeth, sinuses, stools, etc., failed to reveal any cause for her troubles. The ragweed tests were discounted because of the time of year. Dr W H Smith thought that "there is a very large nervous element in the case which probably accounts for most of the trouble."

She died on September 2, probably of inanition. There was no necropsy.

Two cases seemed associated with circumstances possibly disagreeable.

CASE 71—One of these was a medical student, aged 29, who had asthma for six years, only in isolated attacks, continuing from five to ten days, when he first begins his summer work in a shoe factory. It has never lasted longer than this, although he works in the same factory all summer. He has never had hay fever. Skin tests are absolutely negative. There is no trouble at other seasons of the year, and his family history is negative.

CASE 151—Another example may be a marine engineer, aged 46, who had asthma for six years, which came on only when he went ashore. He can go ashore and stay from four to five days without trouble, but if he has a cold he is sure to have asthma. If he has a cold at sea, he will never have asthma. This last fact argues against any infectious origin of his asthma, although his "colds" at sea may not be "colds" in the sense of a bacterial invasion.

EFFECT OF OPERATIONS UNDER ETHER

Three patients gave a history of previous operations under ether, following which there was in each case a distinct improvement in their asthma.

CASE 15—A woman, aged 38, who had asthma in attacks for four years, and in this work so far unclassified, had a tonsillectomy, within a year following which her asthma was indistinctly better for two or three months, but since then has been as bad as ever.

CASE 125—A woman, aged 43, had asthma since the age of 15, had several operations on her nose, and a year ago had the uterus and both ovaries removed. Her asthma improved for a time after this operation, and then relapsed. She is grouped here under "bronchitis."

CASE 84—A woman, aged 30, with asthma for two years, was found to have a rather large ovarian cyst. This was removed. Her asthma improved at once after the operation, and so remarkably that there seemed to be no doubt that the cause had been located. About a month after discharge from the hospital, she came in again with the same original symptoms.

It is, of course, unfortunate that skin tests were not made with the cyst fluid in Case 84. Had they been positive in her and negative

in a number of other control persons, important information would have been obtained

It hardly seems reasonable to think, either in Case 125 or in Case 84, that the cause of the asthma was removed, the very fact that they relapsed again would show the cause to be still present. Why then, should they improve after the operation, and is it not reasonable to think that the administration of ether or the anesthesia itself, had some important effect? It would certainly be interesting to administer complete ether anesthesia to stubborn cases, such, for example, as Case 70 (Refer to the heading "Nervous Asthma")

ECZEMA

Within the past two years interest has been shown in the possible explanation of eczema as a manifestation of anaphylaxis, and the association of eczema with asthma has, therefore, been studied in these 150 cases

Blackfan³⁹ in studying eczema, finds that positive skin tests occur in the great majority of cases of eczema, while they occur only very rarely in the normal control

He finds an early history of eczema in asthma patients, but he cannot prove the relation of eczema to anaphylaxis. He was unable to demonstrate circulating antibodies to the antigen in the blood serum of any patient giving a positive skin test to that antigen

The relation of eczema to anaphylaxis is also mentioned by Schloss⁴⁰

Strickler and Goldberg⁴¹ had twelve cases of eczema, six of which gave a positive skin test to one or more proteins

Talbot⁴² divides eczema in children into two groups, one of which depends on anaphylaxis

White⁴³ also comments on the relationship of eczema to anaphylaxis

In the present series, only six cases gave a history of eczema. Four of these were children (Cases 117, 123, 144 and 150), who had had eczema as babies, and three of whom had it with asthma. The fourth (Case 117) has had no further eczema, but asthma continues now for upward of nine years. Each of these four children gave one

39 Blackfan, K D. *Am Jour Dis Child*, 1916, **11**, 441

40 Schloss, O M. *Arch Pediat*, 1916, **33**, 210

41 Strickler and Goldberg. *Anaphylactic Food Reactions in Dermatology*, *Jour Am Med Assn*, 1916, **66**, 249

42 Talbot. *Tr Am Pediat Soc*, 1916, **28**, 190

43 White, C J. *Anaphylactic Phenomena in Eczema*, *Jour Cutan Dis*, 1916, **34**, 55. *The Treatment of Eczema in Childhood*, *Boston Med and Surg Jour*, 1918, **178**, 5

or more positive skin tests Under "Diet" is a discussion of one of them (Case 117) in which the eczema was not influenced by the total omission of egg, to which alone of several proteins, she gave a skin test The other three children reacted to the pollens, but the eczema was not worse in the autumn, and consequently the tests are disregarded

Two patients (Cases 6 and 46) were adults, aged 43 and 40, respectively, with "winter" asthma for eighteen and two years, respectively, but they had had eczema for only six and one years The connection between the asthma and eczema would, therefore, seem to be not a close one

DISCUSSION

It is obvious that there are many different exciting causes of bronchial asthma It is obvious that to discover the exciting cause in any patient requires considerable study, and finally, it is very striking to note that, in the whole series, there are no two cases which are even closely alike

Separation of these patients into groups has been attempted and accomplished as accurately as possible It often has been very difficult to group the individual patient, and he has been so grouped only when, after conscientious study, including as careful "following up" as was possible, it has seemed reasonable to do so

A survey of 150 cases in this present report shows the following statistics The age of the patients varies from 3 to 74, although there are only twenty-two patients who are below the age of 15 There were seventy-six males and seventy-four females The onset of asthma occurred in the following age groups Below 10, forty-two, between 10 and 20, twenty-eight, above 20, eighty, above 40, twenty-one

Twenty-eight per cent of the cases being classed as "extrinsic" is, apparently, a very small proportion Perhaps further skin tests might have brought out further extrinsic causes The possibility of susceptibility to feathers, to various dusts, powders and perfumes, and to various foods, has been kept constantly in mind, and yet it has not seemed reasonable to attribute the cause of asthma to these substances in any one of the 150 patients in this particular series

These figures cannot well be compared with those of other authors because it is almost impossible to lay down definite criteria for the various groups Careful consideration of the many factors has been the only means of classification To see or to hear from the patient again after a period of several months has been a very great assistance in checking up the original impression and classification Of 150 patients, all but twenty-six were seen more than once, twenty-five

patients have been followed for over a period of two months, thirty-three for over six months, and thirty-six for a period of over a year

Table 10 represents a summary of the whole series. Aside from the eosinophil counts there are a number of striking observations. The average age at onset of extrinsic asthma is 12, or less than half the average age at onset of intrinsic asthma. There are about twice as many cases of intrinsic as of extrinsic asthma.

The family history is here very important and interesting. There was a history of either asthma, hay fever, hives or violent poisoning from food in forty-four of this group of patients, twenty-seven on the mother's side, and two on both, not stated in thirty-three. Fifty-eight per cent of the cases of extrinsic asthma gave a positive family history, while only 10.5 per cent of the cases of intrinsic asthma gave such a history. Attention is here called to the figures of R. A. Cooke, who, as was stated, found a positive family history in 48.4 per cent of his cases of sensitization, which may be compared to the 58.7 per cent positive family history in cases of extrinsic asthma in this report.

From this we may say that a positive family history indicates the probability of a particular case of asthma belonging to the extrinsic rather than to the intrinsic group.

The most important problem in the study of asthma, and, at the same time, the one most difficult to approach, is, "Why are these people sensitive?" Effort has been made to discover whether there was any one factor common to all cases of asthma, some abnormality of anatomy or physiology present in these patients and not present in normal people. Such an abnormality would explain why certain individuals were susceptible to foreign proteins, and others were not.

The blood picture is one possibility inasmuch as an eosinophilia is said to occur commonly in asthma.

Differential blood counts have been done in 113 of these 150 patients, during the attacks in sixty-seven, and between the attacks in fifty-six, both in and between in twenty-one. In many patients several smears were counted.

According to Staubli²⁵ eosinophils decrease after the administration of adrenalin, but all cases are here included.

Total leukocyte counts were done in only twenty-two patients—a number too small from which to draw conclusions, except to show that, on the whole, the differential count gives a fair idea of the absolute numbers of these cells.

In nearly every smear 300 cells were counted. Wright's stain was used. Consideration of all these counts together shows that during the attacks the eosinophils averaged 5.3 per cent, between the attacks they averaged 5 per cent. (The patients were considered to be in an attack when sibilant râles were heard in the lungs.)

According to various textbooks, the normal percentage of eosinophils varies from 2 to 4 per cent. The percentage in asthma is, therefore, somewhat above the normal.

As is seen by Table 10, the averages, both for extrinsic and intrinsic asthma, are not very different. If anything, the counts made from patients with intrinsic asthma seem to be higher. Of more significance than this, however, is the absence of any important difference in the average of counts made during and between attacks.

In the twenty-one patients who were studied, both during and between the attacks, the eosinophils averaged 7.2 per cent during the attacks (twenty-four smears) and 5.3 per cent between attacks (twenty-four smears). Although in three patients the percentage of eosinophils was over twice as great between the attacks as during them.

Attention is also called to the columns on Table 10 showing the greatest percentage of eosinophils seen in the various groups. Here again, there is very little difference seen in counts made during and between attacks. In several cases counts were made at fairly frequent intervals during and after the attack, and no important and sudden change in the percentage of eosinophils at any particular time related to the attack was observed. It must be admitted, however, that not yet have sufficient observations been made on this point.

It may then be concluded that in human asthma there is no such constant variation in the percentages of eosinophilic leukocytes in the blood as is seen in experimental anaphylaxis in animals. The presence of an eosinophilia in asthma is confirmed, but its significance is not understood. Furthermore, it does not occur to a greater extent in those cases in which a resemblance to anaphylaxis exists, than in the others.

Further study is necessary before we can tell why these people are sensitive.

There is always a great temptation to regard asthma as an expression of some disturbance of the nervous system. This would explain the dissimilarity of the cases, even among those in the same group and would explain the behavior of many cases under circumstances which should theoretically have no significance. A few of the more striking examples have already been discussed under nervous asthma. But the great difficulty is that, on the other hand, there are many authentic cases, all with extrinsic asthma, who have had asthma come on when exposure to the antigen was sudden, and not at all anticipated, and there are many cases, some in this present series, in which a definite attack of asthma has been artificially produced by the injection of either ragweed pollen or horse hair extracts to which the patient was sensitive. It seems hard to explain how any "nervous" or any hysterical state, could explain this last condition.

TABLE 10—SUMMARY OF THE WHOLE SERIES OF CASES

Group	Number Cases	Per Cent Cases	Male Female	Average Age at Onset	Average Duration in Years	Positive Family History in per Cent	Eosinophilla							
							In Attack				Between Attacks			
							Number Cases Counted	Number Smears	Average Per centage	Greatest Per centage	Number Cases Counted	Number Smears	Average Per centage	Greatest Per centage
Pure pollen asthma	12	8	7 5	19 2	6 9	56	3	3	7	12	7	10	3	6 6
Complicated pollen asthma	12	8	5 7	3 2	8 4	45	7	13	5	10	8	10	5 3	10
Horse asthma	16	10 51	6 10	14 5	13 2	68	6	11	4 5	11	10	17	5 3	11
Acute food asthma	2	1 33	1 1	1 0	12 4	100	0				1	2	3 4	4 6
Summary extrinsic asthma	42	28	19 23	12 0	10 1	58 7	16	27	5	12	26	39	4 6	11 0
Gastrointestinal	5	3 33	5 0	19 0	14 4	0	3	4	4	4 6	2	2	3 5	4 0
Bronchitis	21	16	12 12	17 9	11 0	13	7	10	8 1	13 3	11	12	5 2	11 0
Winter asthma	12	8	9 8	43 2	6 7	10	4	5	3 6	11 3	3	3	3 3	5 3
Emphysema, chronic bronchitis	18	12	5 13	34 0	7 5	6 7	12	19	4 3	13	2	4	8 25	14 0
Tuberculosis	6	4	5 1	16 1	12 8	16 6	4	9	4 9	10	0			
Nose and teeth	4	2 60	4 0	25 0	19 25	0 6	3	4	5	9	1	2	10 5	13
Miscellaneous	10	6 66	2 8	23 8	6 7	11 1	4	8	6 25	13	4	6	4 8	12
Summary intrinsic asthma	79	52 64	42 37	26 05	9 86	10 5	37	59	5 4	13	23	29	5 5	14
Unclassified	29	19 36	15 14	21 3	9 2	28	14	20	5 3	15 6	7	10	4 4	11
Total	150	100	76 74	21 1	10 0	27 2	67	10 6	5 27	15 6	56	78	5 03	14

Attention is called to the fact that asthma has been already described⁴⁴ as one symptom of the condition known as vagotonia, in which there is a heightened tonus in the "vagal" or crano-sacral autonomic system of nerves, and that another sign of this condition is an increase of the eosinophil cells. Further study on this point would be very important and might readily reveal that disturbance of physiology which theoretically is common to every case of the disease, and which would explain all forms of the disease which we now call bronchial asthma.

TREATMENT

The treatment of bronchial asthma resolves itself into the treatment of the exciting cause if this can be identified. The treatment of many individual cases has already been discussed in the body of the paper.

The best results are obtained in the cases of extrinsic asthma, especially in pollen cases. Treatment with an extract of the specific pollen will relieve the hay fever and the asthma often entirely. Specific treatment of the horse asthma cases is usually only partially successful, although the results obtained justify the effort.

The question of dosage as well as the time interval between doses is, of course, important but discussion of these factors must be based on a much larger series of cases. The general impression here has been that relatively small doses only sufficient to cause a noticeable local reaction on the arm persisting for twelve hours and given not more often than once in five days, has given the best result. The doses have been continued for at least twenty-five days after the asthma has abated.

Throughout this work the dosage has been measured in milligrams of total nitrogen — not in quantities of solutions.

There has been no experience with specific treatment of other extrinsic causes but avoidance of the particular protein has usually been possible and satisfactory.

The treatment of intrinsic asthma is far from satisfactory. Local treatment of the nose, throat and teeth has been long considered important. The removal of nasal polypi, the drainage of sinuses and the extraction of teeth will all relieve the asthma. This relief, however, rarely amounts to a cure and even if very marked is rarely permanent. The fact that many patients have spontaneous intervals of freedom from asthma which last for months or years, makes the results of any treatment difficult of interpretation.

The use of vaccines in the cases presumably due to bronchial infection whether or not these infections are accompanied by emphy-

44 Barker, L. F. *Canad Med Assn Jour*, 1913, **1**.

sema and the study of the bacterial flora in the sputum from these cases must be left for some future time

In following these 150 cases, it has been a matter of the greatest interest to discover why periods of improvement have taken place. In most cases, no reason for this could be discovered. All of which suggests the marked nervous or autonomic element which doubtless exists. One patient who had been listed under chronic bronchitis and emphysema remained free of asthma, in spite of a continued cough for eleven months following exactly from the day of performing the various intradermal skin tests on his arm — which tests had been all negative.

Potassium iodid remains, as Lemann⁴⁵ puts it, the "sheet anchor" in the treatment of asthma. It is especially effective in cases whose asthma depends on a bronchitic infection.

Calcium salts were used in asthma by Kayser,⁴⁶ and in the present series have undoubtedly helped some cases.

Adrenalin is a very important drug in the treatment of asthma, a subcutaneous injection of adrenalin chlorid solution (Parke, Davis and Co.) will control the attack in almost every case. It, however, has relatively little effect on the general control of the disease. There is much literature on the use of adrenalin in asthma. The theories of its use are discussed by von Jagic⁴⁷. Ephraim⁴⁸ has watched its effect through a bronchoscope. Staubli⁴⁹ recommends its use as a very fine spray and describes an atomizer for this purpose for which he claims more permanent results than by simpler methods of administration.

Asthma powders of various kinds, most of which contain niter and stramonium leaves, all help the attack, but do not cure. The treatment of associated conditions,⁵⁰ constipation, hyperacidity, etc., is always important, and the writer has seen more than one case very markedly improved on regular doses of a mild alkaline aperient salt.

Frequently unsuspected and apparently unimportant suggestions, such as a temporary change of residence, a slight temporary modification of the diet, ether anesthesia, temporary rest in bed with full diet, correction of faulty attitude, etc., have been of the greatest assistance, and not infrequently have led to a virtual cure. On all these various

45 Lemann, I. I. Treatment of Bronchial Asthma, *Am Jour Med Sc*, 1911, **142**, 781.

46 Kayser, C. *Therap Monatsh*, 1911, **26**, 157.

47 Von Jagic. *Berl klin Wchnschr*, 1909.

48 Ephraim. *Deutsch med Wchnschr*, 1912, **38**, 1453.

49 Staubli. *Munchen med Wchnschr*, 1913, **60**, 113.

50 Ebstein, W. *Deutsch med Wchnschr*, 1911, **38**, 1921.

methods there is rarely any good control, because so many patients have intervals of freedom from attacks, which intervals may last for several years

CONCLUSIONS

1 "Bronchial asthma" is a symptom of some other diseased condition

2 One hundred and fifty cases of asthma can nearly all be divided, according to the etiology of their attacks, into various subgroups under the general headings of "extrinsic asthma" and "intrinsic asthma"

3 Extrinsic asthma includes 28 per cent, intrinsic asthma includes 53 per cent of the entire group — the other 19 per cent being unclassified

4 The age at onset of extrinsic asthma averages about 12 years, while the age at onset of intrinsic asthma averages about 26 years

5 A history of either asthma, hay fever or food poisoning, in the immediate family, occurs in 58.7 per cent of the cases of extrinsic asthma, but in only 10.5 per cent of the cases of intrinsic asthma

6 Skin tests are of great assistance in confirming the diagnosis

7 Skin tests alone are of no value unless reasonably compatible with the patient's history or experience

8 A positive skin test is a necessary preliminary to successful specific treatment

9 The "nervous" element is very important in asthma, but probably does not explain why certain individuals have asthma

10 The percentage of eosinophilic leukocytes in the blood is increased in asthma, the degree of this increase is not different in extrinsic or intrinsic asthma, nor does it vary during and between the attacks

11 Treatment resolves itself into the treatment of the exciting cause. Various different therapeutic procedures sometimes yield favorable results, but these cannot be explained

12 The real problem — what is the fundamental disturbance of anatomy or physiology which expresses itself by attacks of asthma — remains unsolved

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CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

L STUDIES ON THE CONTROL OF HUNGER BY DRUGS *

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CHICAGO

The hunger mechanism is a local mechanism within the stomach itself, subject to central regulation. A great accumulation of well established data points to the fact that hunger is a sensation produced by an increase in intragastric tension¹. This is produced by characteristic contractions of the empty or nearly empty stomach beginning in the fundic region. Physical attitudes and local pathologic conditions, as ulcer or pyloric constriction, interpret tension as pain².

Stomach activity is influenced by peripheral nervous control³. The vagus nerve carries impulses stimulating tone and peristalsis, the splanchnics contain inhibitory fibers. By these two paths central action is exerted. It has been found, however, that with both vagi and splanchnics sectioned the stomach regains the tone temporarily lost, and the typical muscular activity of the stomach is resumed. This suggests a mechanism inherent in the stomach itself which regulates motor activity. The anatomic basis of such a system may be found in a nodal system which Keith⁴ has recently described in the stomach wall comparable to the nodal system of the heart.

Manipulation of the hunger contractions has been carried out by changing mental states and the administration of various substances. Excitement, fear and anger inhibit hunger⁵. This comes well within the experience of the individual. Tracings from the stomach demonstrate that the hunger contractions in these conditions are inhibited. Water, acids, alkalis, and food taken by mouth or placed directly into

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† Mr Ginsburg died during the course of the work for which he furnished the inspiration

1 Carlson *Am Jour Physiol*, 1913, **31**, 175

2 Hertz *Sensibility of the Alimentary Canal*, London, 1913, p 47. Ginsburg, Tumpowsky and Hamburger *Jour Am Med Assn*, 1916, **67**, 990. Hardt *Jour Am Med Assn*, 1918, **70**, 837

3 Carlson *Am Jour Physiol*, 1913, **32**, 369

4 Keith *Lancet*, London, 1915, **2**, 371

5 Carlson *Am Jour Physiol*, 1913, **32**, 376

the stomach by tube or through a fistula also inhibit contractions⁶ Fever associated with anorexia inhibits contractions,⁷ while in the cachexia of advanced pulmonary tuberculosis with chronically high temperature they may be extremely vigorous⁸ In starvation⁹ and experimental pancreatic diabetes¹⁰ contractions are marked The effects of drugs on stomach activity has not been emphasized nearly to the degree that the intestine has been studied from this standpoint Some facts in this regard have already been established clinically The present work was undertaken to determine the effects of various common drugs on the hunger contractions by the use of the balloon method

EXPERIMENTAL METHODS

Gastric fistulae were produced in twelve dogs, and in four of these both vagi and splanchnics were cut In the latter cases it has been found advisable to section the splanchnics first, inasmuch as this part of the preparation is the most difficult and attended with the greatest fatality The major splanchnic is severed as it emerges from the diaphragm On the left side it lies lateral to the adrenal, running toward the gland parallel with the large adrenal vein The right splanchnic is more difficult to obtain because the liver hampers good exposure and the nerve very frequently lies beneath the vena cava Hemorrhage from the many small retroperitoneal veins about the adrenal makes the operation more difficult because other structures are easily mistaken for the nerve Occasionally pneumothorax is produced by exploring the edge of the diaphragm, but this is not fatal In about two weeks the vagi may be severed Incision is made in the eighth or ninth interspace on the left side and somewhat posteriorly The esophagus is hooked up through the interspace, the right and left vagus lying posteriorly and anteriorly, respectively, are grasped in a hemostat and a piece excised All branches are similarly treated, and the wound is quickly closed If the operation is done hurriedly, that is to say, two or three minutes elapsing from opening to closure of the pleural cavity, artificial respiration is not necessary In fact, we used artificial respiration but twice, and lost but one animal at this stage, an accident which, with the technic developed subsequently, might have been avoided If the animal shows signs of difficulty the edges of the wound may be approximated with the fingers until respirations become more regular, and the operation may then pro-

6 Carlson *Am Jour Physiol*, 1912, **31**, 151, and 1913, **32**, 389

7 Meyer and Carlson *Am Jour Physiol*, 1917, **44**, 222

8 Meyer, Jacob Contribution, Hunger in Tuberculosis, to be published

9 Carlson *Am Jour Physiol*, 1914, **33**, 95

10 Luckhardt *Am Jour Physiol*, 1914, **33**, 313 Luckhardt and Hamburger *Jour Am Med Assn*, **66**, 1831

ceed In one case the heart stopped pulsating for about one minute By rapid and vigorous massage of the heart directly with two fingers through the intercostal space to imitate as nearly as possible the force and rate of the heart, pulsations recovered slowly and very feebly at first, finally at the usual rate and strength as near as one could determine The dog recovered and lived many weeks, dying from respiratory infection This result could not be repeated in other conditions and was probably due to recovery from reflex stimulation of the vagus The gastric fistula was made through the left rectus to make use of the valve action of that muscle A cone of stomach was drawn through the opening and the serosa stitched to the peritoneum, fascia and skin by three or four stitches in each layer The apex was opened and the mucosa tacked to the serosa by three loose stitches

The drugs were used on both sets of animals, those with the "intact" stomach having the nerves intact, and those with the "isolated" stomach having the peripheral nerves sectioned The animals were easily trained to lie on the laboratory tables in a moderately darkened room with a towel covering the head to keep out the light and prevent their disturbance from such outside factors as the presence of others in the laboratory and the manipulations of the observer It was possible in this way to have four animals running together while a single observer manipulated the kymographs, administered the drugs and recorded observations One finds that the dogs will lie on the plain, uncovered table, not requiring soft blankets They become so accustomed to the routine that they choose the proper laboratory by preference when released from the kennels, and lie quietly until the balloon is removed from the stomach at the end of the observation, when they sense their liberty and jump from the table The animals are so astonishingly quiet during observations that other workers coming into the room unfamiliar with the work think the dogs are anesthetized Subcutaneous and even intravenous injections may be made without disturbing the animal One can, unassisted, apply the constrictor to the leg, plunge the needle into the vein, remove the constrictor and inject without causing the animal to change his position Hypodermic and intramuscular injections require no assistance

RESULTS

Atropin—Auer and Meltzer¹¹ assert that atropin causes paralysis of the vagus endings connected with the ganglia of Auerbach's plexus and that the action is on the myoneural junction Cushny¹² believes that the terminations are not paralyzed, because small doses only arrest

¹¹ Auer and Meltzer *Am Jour Physiol*, 1906, **17**, 17

¹² Cushny *Pharmacology and Therapeutics*, Philadelphia and London, 1913

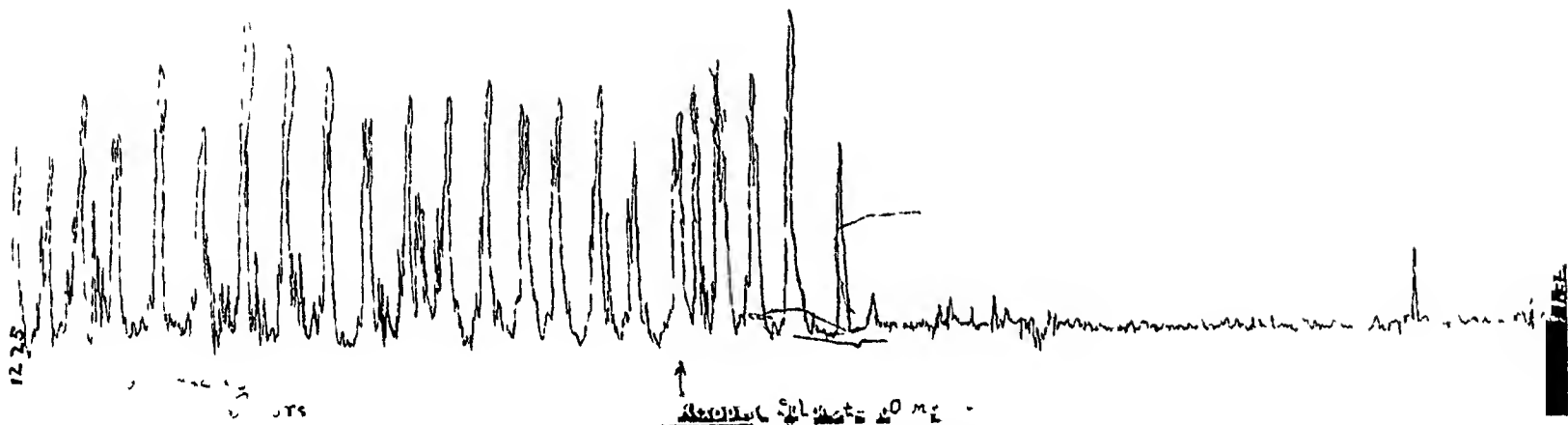


Fig 1—Atropin, $\frac{1}{80}$ grain subcutaneously, causing complete inhibition in seven minutes lasting hours

certain abnormal violent forms of contractions without interfering with normal peristalsis. He also says that larger doses increase, and very large doses paralyze, the latter probably never occurring in the intact animal. Clinically, belladonna relieves some spasmodic conditions of the stomach by paralyzing the vagus and allowing unopposed action of the splanchnics.¹³ Fluoroscopic examination has shown that

TABLE 1—ATROPIN

Stomach	Adminis- tration	Dose, Grain	Result	Latent Interval Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1/80	Inhibition	7		
Intact	Subcuta- neous	1/80	Inhibition	10		
Intact	Subcuta- neous	1/80	Inhibition	14		Eserin, 1/80 grain given 23 minutes after inhibition began yielded contractions in 23 minutes
Intact	Subcuta- neous	1/70	Inhibition	8	3 hrs 40 min then contractions	Occasional contractions "escaped"
Intact	Subcuta- neous	1/70	Inhibition	5		
Intact	Subcuta- neous	1/60	Inhibition	7	1 hr 40 min +	
Intact	Subcuta- neous	1/60	Inhibition	5	1 hr +	23 minutes after pilocarpin 1/6 grain
Intact	Subcuta- neous	1/60	Inhibition	5		1 hour 20 minutes after eserine 1/60 grain
Intact	Subcuta- neous	1/50	Inhibition	4	20 min +	
Intact	Subcuta- neous	1/100	Inhibition	8		50 minutes after pilocarpin 1/12 grain
"Isolated"	Subcuta- neous	1/50	Inhibition	8	1 hr +	17 minutes after pilocarpin 1/6 grain
"Isolated"	Subcuta- neous	1/40	Inhibition	8	4 hrs +	Pituitary extract (Armour) ampule intravenously, 3 hours after followed by small infrequent contractions
"Isolated"	Subcuta- neous	1/40	Inhibition	10	1 hr 20 min --	1 hour 32 minutes after pilocarpin 1/6 grain

often the spasm is suddenly relieved, while in other cases shown to be spasmodic by the massage test, it has no effect. Hertz¹⁴ says that belladonna is remarkably efficient in hour glass contractions of spasmodic origin and may even relieve spasm in the presence of active ulceration. In our work atropin sulphate in doses from 1/80 to 1/40 grain hypodermically invariably inhibited contractions and counteracted the

¹³ Barclay Alimentary Tract. A Radiographic Study, New York, 1915, p 17

¹⁴ Hertz See reference Footnote 2, p 76

effect of pilocarpin and eserine in this regard. The time of action is quite constantly between five and ten minutes. The inhibition is sudden, decisive and persists for hours. Occasionally a few undulations "escape." Otherwise the tracing records only the respiratory oscillations. The fact that the same results obtain in "isolated" stomach indicates that the action is on the myoneural junction.

TABLE 2—PILOCARPIN

Stomach	Administration	Dose, Grain	Result	Latent Interval, Minutes	Duration of Effect	Remarks
Intact	Subcutaneous	1/5	Increased tonus	8	20 min	35 minutes after epinephrin (adrenalin), 2 cc 1:10,000 intravenously and subcutaneously
Intact	Subcutaneous	1/5	Contractions	5	45 min +	
{ Intact	Subcutaneous	1/75	No effect			Gradual increase after second dose
{ Intact	Subcutaneous	1/75	Slight increase		2 hrs +	
Intact	Subcutaneous	1/6	Contractions	8	1 hr 30 min +	Gradual increase in tonus preceded the contractions, later inhibited by atropin
Intact	Subcutaneous	1/12	Contractions	15	50 min	Inhibited by subsequent atropin
Intact	Subcutaneous	1/12	Contractions	9		40 minutes after pituitary extract
"Isolated"	Subcutaneous	1/6	Contractions	8	1 hr 30 min +	Increase in tonus preceded contractions, inhibited by subsequent atropin
"Isolated"	Subcutaneous	1/5	Contractions	6	1 hr	46 minutes after eserine 1/40 grain
"Isolated"	Subcutaneous	1/6	Contractions	3		Inhibited by atropin 20 minutes later

Pilocarpin—Sollmann¹⁵ says that the myoneural junctions paralyzed by atropin are stimulated by pilocarpin. In doses from $\frac{1}{12}$ to $\frac{1}{5}$ grain hypodermically the contractions are augmented, accompanied by diminished pulse rate. With the change in pulse rate as a criterion for absorption it could be determined that absorption occurred in seven to ten minutes. The contractions were inhibited by subsequent atropin in the usual five to ten minutes. The same effect was noted with section of the nerves, confirming Sollmann's opinion that pilocarpin is effective even after degeneration of the nerves.

Eserine—Stimulation is produced by eserine, particularly by intravenous administration. In subcutaneous injections there is often a long latent period before activity begins, but activity remains as long as four hours. Again, as with pilocarpin, coincident with the gastric

15 Sollmann Manual of Pharmacology, 1917, p 299

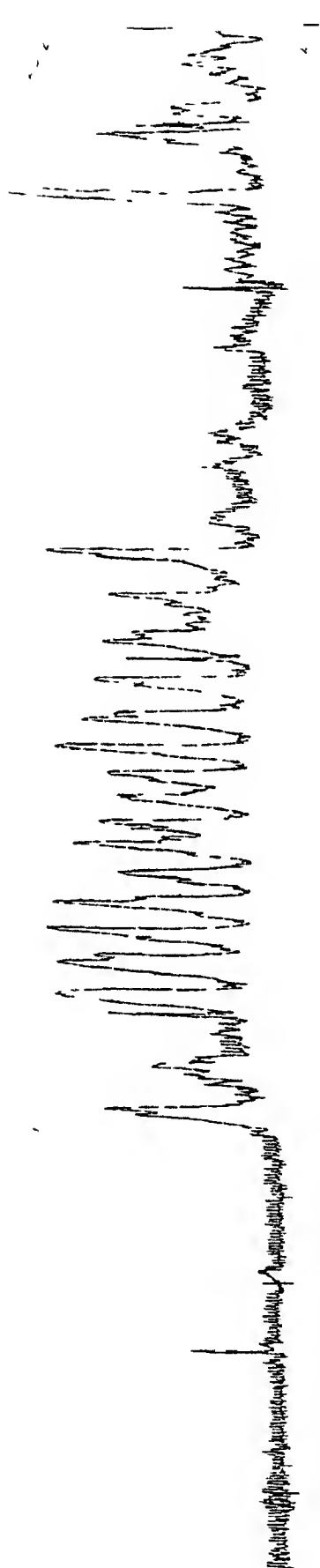


Fig 2A—Eserin, $\frac{1}{60}$ grain subcutaneously, causing marked contractions lasting an hour and a half

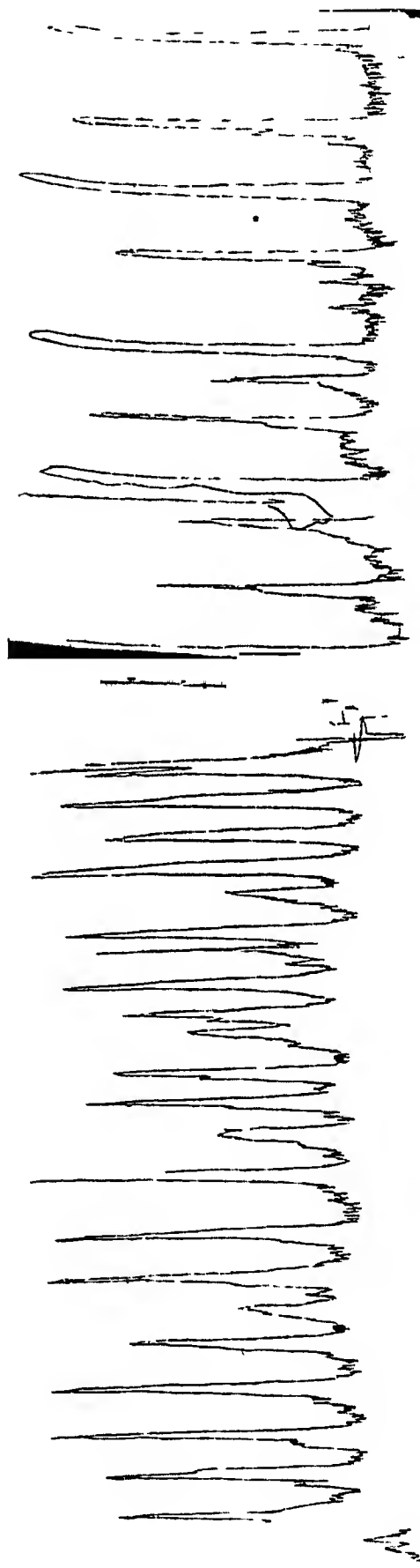


Figure 2B

manifestations, in the experiments the pulse rate fell as low as 50 beats per minute, and gradually returned to normal with abolition of the gastric effects. Inasmuch as similar effects were obtained on the "isolated" stomach, the work confirms the belief that eserine also acts on the nerve endings.

TABLE 3—ESERIN

Stomach	Adminis- tration	Dose, Grain	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1/60	Contra- ctions	6	1 hr 30 min +	For 1 hour contractions unusually strong
Intact	Subcuta- neous	1/100	Contra- ctions	6	2 hrs +	
Intact	Subcuta- neous	1/50	Contra- ctions	2	40 min	Very strong contractions, may have been oncoming regular period
Intact	Subcuta- neous	1/60	Contra- ctions			
Intact	Subcuta- neous	1/60	No contra- ctions			Administered 19 minutes after atropin 1/60 grain
Intact	Subcuta- neous	1/60	Contra- ctions	6	1 hr 35 min	Inhibited by atropin
Intact	Subcuta- neous	1/100	Contra- ctions	5		
Intact	Subcuta- neous	1/80	Contra- ctions	20	30 min	37 minutes after atropin 1/80 grain
Intact	Subcuta- neous	1/80	Contra- ctions	23	4 min	2 hours 32 minutes after preceding eserine
Intact	Subcuta- neous	1/60	Contra- ctions	14	12 min	39 minutes after preced- ing eserine
Intact	Intrave- nous	1/100	Contra- ctions	5		Moderate increase with tonus undulations
Intact	Intrave- nous	1/100	Contra- ctions	4		Large tonus undulation
"Isolated"	Intrave- nous	1/100	Contra- ctions	35		Periodic sequence
"Isolated"	Intrave- nous	1/50	Contra- ctions	7	4 hrs +	Marked increase
"Isolated"	Subcuta- neous	1/40	Contra- ctions	5		Increased tonus
"Isolated"	Subcuta- neous	1/40	Contra- ctions	15	2 hrs +	
"Isolated"	Subcuta- neous	1/50	Contra- ctions	5	3 hrs 15 min +	
"Isolated"	Subcuta- neous	1/40	Slight con- tractions	20		

Cocain—In general, it is asserted that cocaine first stimulates, then depresses smooth muscle regardless of innervation.¹⁶ Cushny¹⁷ believes that it paralyzes the local nervous mechanism. Profound inhibition occurs with doses of 1 cc of 0.5 per cent solution of cocaine per

¹⁶ Sollmann Manual of Pharmacology, 1917, p 252

¹⁷ Cushny Pharmacology and Therapeutics, 1913, p 308

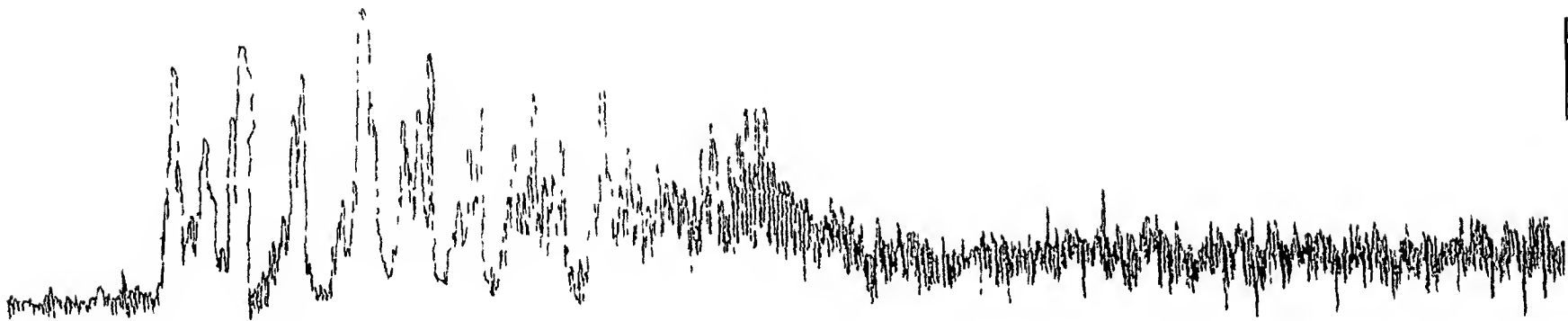


Fig 3—Cocain, 1 cc of 1 per cent per kilogram subcutaneously, causing profound inhibition lasting over two hours

kilogram The tracings give a striking picture demonstrating why cocaine allays the hunger pangs

TABLE 4—COCAINE

Stomach	Adminis- tration	Dose	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Intrave- nous	3 cc 0.5% 7.8 kg	Inhibition	1	30 min +	Lowered tonus, increased respiratory rate
Intact	Subcuta- neous	1 cc 0.5% per kg	Inhibition	10	2 hrs +	Lowered tonus, active period shortened
Intact	Subcuta- neous	1 cc 0.5% per kg 14 cc	Inhibition	26	1 hr 30 min +	Given in active period, preliminary rise in tonus and contractions, then lowered tonus and con- tractions and increased respirations
Intact	Subcuta- neous	0.5 cc 1% per kg 5 cc	Slight in- hibition	45	1 hr +	Given in moderately ac- tive period, low degree contractions
Intact	Subcuta- neous	1 cc 1% per kg 9.2 cc	Inhibition	15	2 hrs +	Marked salivation, ani- mal licking nose
Intact	Subcuta- neous	1 cc 1% per kg 8 cc	Inhibition	10	2 hrs 30 min +	Never regains usual vig- orous contractions
Intact	Subcuta- neous	1 cc 1% per kg 7 cc	Inhibition			Gradually appearing low- ered tonus and increased respirations
Intact	Subcuta- neous	1 cc 1% per kg 11 cc	Inhibition	18	2 hrs +	Marked result
Intact	Subcuta- neous	1 cc 1% per kg 9 cc	Inhibition	6	2 hrs +	Marked result
Intact	Subcuta- neous	1 cc 1% per kg 9.2 cc	Inhibition	10	2 hrs +	Marked result
"Isolated"	Subcuta- neous	1 cc 1% per kg 11 cc	Slight in- hibition	15	2 hrs +	Lowered tonus 15 min- utes, active 30 minutes then rest 2 hrs +
"Isolated"	Subcuta- neous	1 cc 1% per kg 11 cc	Slight in- hibition			Increased tonus at first as if remnant of an ac- tive period, then lowered tonus and inhibition
"Isolated"	Subcuta- neous	0.5 cc 1% per kg 5.5 cc	Slight in- hibition	12	1 hr 30 min +	Increased respiration, lowered tonus, later complete inhibition for 1 hour 30 minutes

Camphor—Camphorated oil was administered to determine whether its stimulating effect on the central nervous system is reflected in any manner in the activity of the stomach. The stimulating effect observed is only obtained when the drug is administered intramuscularly. In large doses the contractions appear to become more frequent and intense, and the period of activity is prolonged.

Strychnin—As widely employed as strychnin is for its tonic value, there has been no experimental evidence for its supposed gastric effect.

TABLE 5—CAMPHOR

Stomach	Adminis- tration	Dose, Grain	Result	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1	No change		Given at beginning of active period contractions began lasting 1 hour 20 minutes
Intact	Subcuta- neous	2	Increased activity	2 hrs +	Given at beginning of increased tonus, contractions began in 4 minutes and lasted 2 hours +
Intact	Intramus- cular	3	No change		Given during rest period and ob- served for 45 minutes
Intact	Intramus- cular	3	Increased and prolonged activity	1 hr +	Given in active period, contrac- tions became more frequent and intense and period prolonged
Intact	Intramus- cular	3	Increased and prolonged activity	1 hr 30 min +	Given in active period, contrac- tions became more frequent and intense and period prolonged
Intact	Intramus- cular	3	Increased and prolonged activity	1 hr 30 min +	Given in active period, contrac- tions became more frequent and intense and period prolonged
Intact	Intramus- cular	3	Increased and prolonged activity	1 hr 30 min +	Given in active period, contrac- tions became more frequent and intense and period prolonged
"Isolated"	Intramus- cular	3	Increased and prolonged activity	2 hrs +	Given in active period, contrac- tions became more frequent and intense and period prolonged
"Isolated"	Intramus- cular	3	Increased and prolonged activity	1 hr 30 min +	Given in active period, contrac- tions became more frequent and intense and period prolonged
"Isolated"	Intramus- cular	3	Contractions	2 hrs +	Given during rest period, contrac- tions began in 10 minutes, lasting 2 hours +

TABLE 6—STRYCHNIN

Stomach	Adminis- tration	Dose, Grain	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1/60	Contrae- tions	5	3 hrs	Increased excitability
Intact	Subcuta- neous	1/60	Contrae- tions	2	1 hr 30 min	Prolonged active period
Intact	Subcuta- neous	1/60	Contrae- tions	5	2 hrs	Moderate but prolonged increase
Intact	Subcuta- neous	1/60	Contrae- tions		45 min	Given in active period, in- creased contractions but diminished when mild spasms began
Intact	Subcuta- neous	1/60	Contrae- tions	15	1 hr	Moderate increase, dimin- ished when spasms began
Intact	Subcuta- neous	1/60	Contrae- tions	5	2 hrs +	Marked increase, given in active phase
Intact	Subcuta- neous	1/90	Contrae- tions	10	1 hr	Given 1 hour after 1 30,000 epinephrin applied to surface of gastric fistula
Intact	Subcuta- neous	1/100	No con- traction			Given 1 hour after 1 30,000 epinephrin to nasal mu- cosa
"Isolated"	Subcuta- neous	1/60	Slight con- traction			Low grade contractions with no definite active or inactive periods for 2½ hours
"Isolated"	Subcuta- neous	1/60	Contrae- tions		1 hr 30 min	Given in active period, increased tonus and con- tractions
"Isolated"	Subcuta- neous	1/60	Contrae- tions	6	1 hr 30 min	
"Isolated"	Subcuta- neous	1/90	Contrae- tions	8	2 hrs	

It is the usual conception that it increases the tone of the centers regulating the gastro-intestinal tract. With doses of $\frac{1}{90}$ to $\frac{1}{60}$ grain subcutaneously, stomach tonus was increased, but at the same time the general excitability of the animal was increased so that the increased height of the writing level may have been due to the increased tonus of the abdominal muscles. At the same time, however, there appears to be a definite increase in the hunger contractions themselves. Pollak¹⁸ says that strychnin probably has no effect in ordinary doses given hypodermically. Direct application to Auerbach's ganglia causes stimulation.¹⁹

TABLE 7—AMYL NITRITE

Stomach	Adminis- tration	Dose, Minims	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Inhala- tion	10	Temporary inhibition	Imme- diate	5 min	Slightly lowered tonus
Intact	Inhala- tion	10	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min	
Intact	Inhala- tion	10	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min	
Intact	Inhala- tion	5	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min	Inhibition while animal struggled against inhaling the drug, but a large contraction, "escaped"
Intact	Inhala- tion	5	Temporary inhibition	Imme- diate		Only one of the regularly appearing contractions was inhibited 15 minutes after preceding dose
Intact	Inhala- tion	5	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min	
Intact	Inhala- tion	5	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min	
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	5 min	Lowered tonus slowly restored
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	5 min	Given in active phase, lowered tonus quickly restored
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate		Persistent low tonus, no contractions
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate		
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	15 min	Given 55 millimeters after preceding dose
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	4 min	
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	10 min	Original tonus very slowly restored

Amyl Nitrite—Hirschfelder²⁰ says that systemic administration of nitrites relaxes the constriction produced by lead salts, although this

18 Pollak Biochem Centralbl, 1910, 10, 199

19 Langley and Magnus Jour Physiol, 1905-1906, 33, 37

20 Hirschfelder Jour Am Med Assn, 1915, 65, 516

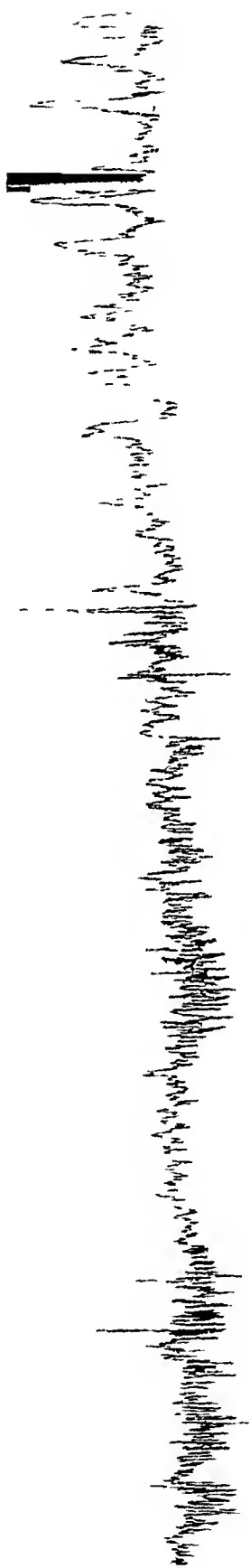


Fig 4—Strychnin, 1/100 grain, subcutaneously, causing increase in tonus and contractions

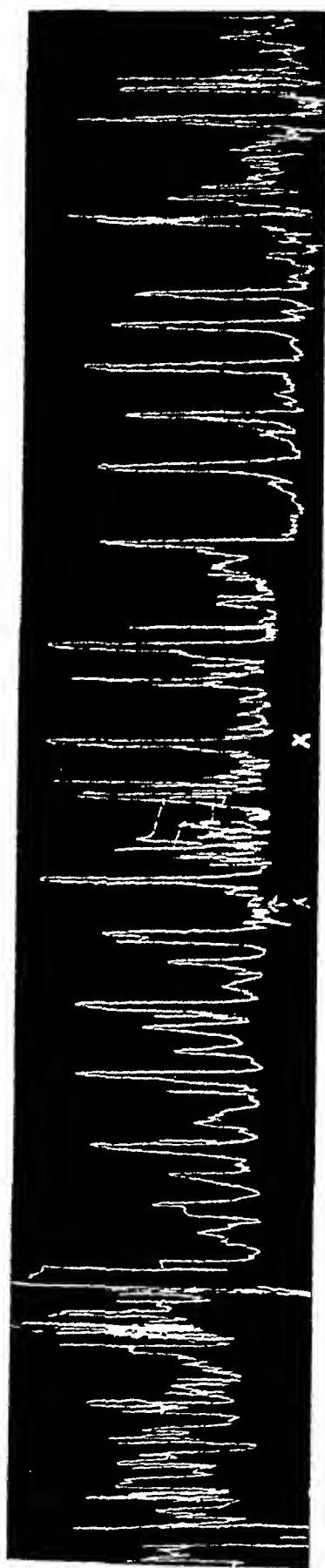


Fig 5—Amyl nitrite, 5 minims by inhalation, causing only slight temporary inhibition, as shown between X---X

treatment for lead colic is not successful Inhalation of 5-minim pearls often repeated after short intervals causes only a temporary inhibition which disappears as soon as the drug is removed from the nostril The effect may be psychic, but the contractions which follow are not reduced in frequency, intensity or duration In animals with the nerves sectioned the same inhibition is observed, but after removal of the drug the tonus remains depressed for a long time, only gradually returning to its original height

TABLE 8—EPINEPHRIN

Stomach	Adminis- tration	Dose	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Intrave- nous	1 cc 1 10,000	Inhibition	Imme- diate	1 hr +	
Intact	Intrave- nous	1 cc 1 10,000	Inhibition	Imme- diate	1 hr	
Intact	Intrave- nous	1 cc 1 10,000	Inhibition	1		Also lowered tonus
Intact	Intrive- nous and subcut	2 cc 1 10,000	Inhibition	8	2 hrs +	Lowered tonus, later complete inhibition
Intact	Raw sur- face of fistula	1 30,000	Inhibition	3	2 hrs +	Lowered tonus
Intact	Nasal mu- cosa	1 30,000	No effect			
'Isolated'	Subcuta- neous	1 cc 1 10,000	Lowered tonus	10		
"Isolated"	Intrave- nous	10 min 1 10,000	Inhibition	Imme- diate	40 min	
"Isolated"	Intrave- nous	10 min 1 10,000	Inhibition	1	1 hr +	
'Isolated'	Intrave- nous	20 min 1 15,000	Inhibition	2	1 hr	
"Isolated"	Intrave- nous	4 cc 1 25 000	Inhibition	5	1 hr +	Period of tetany pre- ceded inhibition

Epinephrin—Administration of adrenalin (Parke, Davis & Co) causes prompt and marked inhibition of the hunger contractions This action should be expected because of its property of stimulating the nerve endings of the sympathetic system The consequent stimulation of the splanchnic endings counteracts the augmentatory effects acting through the vagi Meyer and Gottlieb²¹ say that epinephrin by mouth and by hypodermic injection is ineffective, and when given intravenously acts only a few minutes Our tracings show that the inhibitory effect on the hunger contractions when the drug is given intravenously may last much longer Enough of a 1 to 30,000 solution was absorbed from the eroded surfaces about the gastric fistula to

21 Meyer and Gottlieb Text Book, Philadelphia and New York, 1914, p 188

cause inhibition Subcutaneous injection gives a slower response Inhibition also occurs with the "isolated" stomach, since it is known that the physiologic nerve endings stimulated by epinephrin do not degenerate on section of the nerves, so that the epinephrin effect may persist for weeks

TABLE 9—ERGOT

Stomach	Adminis- tration	Dose, Ampule	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1	Increased contract	5	1 hr	Increased tonus undula- tions
Intact	Intramus- cular	1	Marked in- crease	21	1 hr 30 min	Unusual steplike rise with great tonus, short rest, then activity
Intact	Intrave- nous	½	No effect			Two large contractions, then inhibition followed by active period
Intact	Intrave- nous	1	Temporary inhibition	1	3 min	Given in active period, subsequent contractions lowered tonus
Intact	Intrave- nous	1	Temporary inhibition	1	3 min	Lowered tonus for 30 min- utes, return of contrac- tions for 2 hours +
Intact	Intrave- nous	1	Temporary inhibition	1	3 min	Lowered tonus following
"Isolated"	Intrave- nous	1	Temporary inhibition	1	3 min	
"Isolated"	Intrave- nous	1	Contra- ctions	1	1 hr 30 min	Almost immediate step like rise with enormous tonus well sustained
"Isolated"	Intrave- nous	½	No effect			
"Isolated"	Intrave- nous	1	Contract	3	2 hrs +	28 minutes after preced- ing, followed by steplike rise lasting 2 hours +
	Subcuta- neous	1	No effect			Given in midst of active period, contractions fol- lowed 1½ hours +

Ergot—It has been found that intravenous injections of the fluid-extract of ergot causes an increase in the spontaneous movements of the alimentary tract²² The motor responsiveness to vagus stimulation was also increased Later, Meltzer and Githens²³ injected 10 mg of ergotoxin into rabbits and obtained the same results Using ampoules of ergot intravenously, we usually obtained a temporary inhibition followed by lowered tonus, although contractions ensued Intramuscular injection in one instance gave a tremendous steplike rise, with extremely high tonus level, followed by a short rest, and then another active period The same observation was made on injection of an ampoule intravenously in an "isolated" stomach twenty-eight minutes after a similar injection of one-half ampoule

22 Meltzer and Auer Am Jour Physiol, 1906, 17, 143

23 Meltzer and Githens Proc Soc Exper Biol and Med, 1916, 13, 87

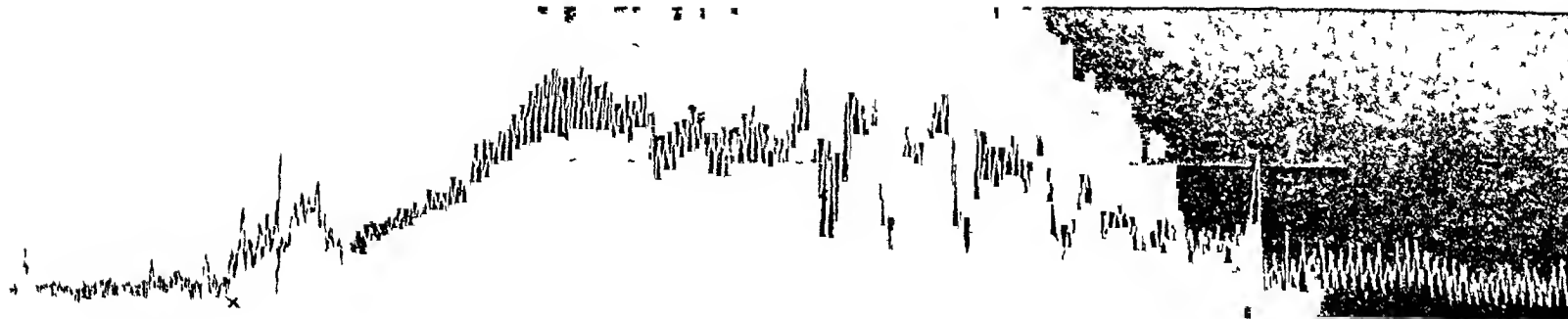


Fig 6—Ergot, 1 ampule intravenously, with almost immediate steplike rise, with well-sustained, marked tonus

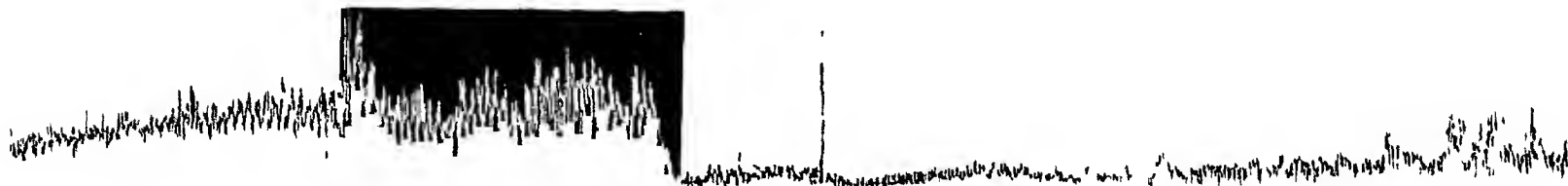


Fig 7—Pituitrin (P D & Co), 3 minims intravenously, with prompt inhibition

Pituitary Extract—It is commonly believed that pituitary extracts stimulate smooth muscle regardless of innervation, and it is given in paralytic distentions²⁴ In the experiments reported the effect of pituitary preparations was remarkably like that of epinephrin Immediately after injection inhibition occurs Parke, Davis & Co's pituitrin and Armour's pituitary liquid were used with similar results, although

TABLE 10—PITUITARY EXTRACT

Stomach	Adminis- tration	Dose	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1 c c (P D Co)	Slight in- hibition	7	30 min +	Given during moderate contractions
Intact	Subcuta- neous	1 c c (Armour)	No effect		30 min	Given in quiescent period
Intact	Intrave- nous	1 c c (P D Co)	Inhibition	Almost Imme- diate	30 min +	
Intact	Intrave- nous	5 min (P D Co)	Inhibition	Almost Imme- diate	1 hr	
Intact	Intrave- nous	3 min (P D Co)	Inhibition	Almost Imme- diate	30 min +	
Intact	Intrave- nous	0.5 c c (Armour)	Inhibition	Almost Imme- diate	30 min	After 30 minutes slowly developing contractions appeared
Intact	Intrave- nous	10 c c (Armour)	Inhibition	Almost Imme- diate	1 hr	Occasional low grade con- tractions appeared
"Isolated"	Subcuta- neous	10 c c (Armour)	No effect			Given in an active period
"Isolated"	Subcuta- neous	10 c c (P D Co)	Inhibition	16		Given in an active period
"Isolated"	Intrave- nous	10 c c (Armour)	No inhibi- tion			Periodic contractions although infrequent, oc- curred after administra- tion
"Isolated"	Intrave- nous	10 c c (P D Co)	Inhibition	Almost Imme- diate	1 hr	Subsequent active period short
"Isolated"	Intrave- nous	10 min (P D Co)	Inhibition	Almost Imme- diate	2 hrs	Given in middle of active period
"Isolated"	Intrave- nous	5 min (P D Co)	Inhibition	Almost Imme- diate	1 hr	Given in beginning of ac- tive period

both preparations caused a rise in blood pressure when tested on crucial animals In accordance with these results are the results of Bayer and Peter,²⁵ who noted that pituitrin and also fresh extract of the pituitary body might inhibit the movements and tone of rabbits' isolated intestinal loop Shamoff²⁶ and Hoskins²⁷ found that the intes-

²⁴ Sollmann Manual of Pharmacology, 1917, p 339

²⁵ Bayer and Peter Arch f exper Path u Pharmacol, 1911, **64**, 209

²⁶ Am Jour Physiol, 1915-1916, **39**, 268

tinal action varies greatly in different preparations, some even relaxing like epinephrin. Even extracts of fresh glands gave this result, although blood pressure tests were normal. The effects of pituitrin were remarkable in their inhibitory effects. Having determined the length of the periods by mere recording without administering the drug, one could observe that administration of pituitrin cut short the active period so that the subsequent rest period equaled the rest period usual for that animal on that particular day plus the "inhibited" portion of the previous active period arrested by pituitrin. By repeating the drug one could predict with surprising accuracy about the time of onset of the next active period. It appears, therefore, that the action of pituitrin is of short duration.

COMMENT

To preserve the conditions of experimentation as nearly constant as possible the records were taken about 1 p. m., running on until about 5 p. m. The dogs were then fed and given nothing else but water until after the next observation at the same hour on the next day. To obtain more accurate results the drugs were given by routes enabling prompt absorption and action so that the change in the picture of gastric motility might be referred to the manipulation. Observations were made for some time before injections to determine whether the stomach was in a period of rest or activity. Only in this way, recording several periods, can the observer decide that he is dealing with the beginning of a rest or active period as the case may be. By observing the periodicity the time interval may be determined so that one may conclude fairly regarding the effects of the drug. For instance, if a drug is administered at the end of an active period the subsequent rest period may be fallaciously ascribed to the drug. In any work involving the hunger contractions it is of prime importance to determine the phase of gastric motility and repeat the manipulation during different phases. There still remains a large field for intensive experimentation with drugs by varying the preparations and dosages, studying the intestinal movements simultaneously and checking results with observations on the other pharmacologic effects of the drug employed, which the exigencies of the present situation prevent the authors from surveying.

Thanks are due Drs. A. J. Carlson and A. B. Luckhardt for their valuable suggestions and Dr. Jacob Meyer and Mr. Seymour Cohen for their kind assistance in part of the work.

REPORT OF A CASE OF PAROXYSMAL TACHYCARDIA
CHARACTERIZED BY UNUSUAL CONTROL
OF THE FAST RHYTHM*

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In view of the fact that the subject of this report possessed to a remarkable degree the power of control over his pathologic rhythm, the following instance of paroxysmal tachycardia in a young adult seemed to us of sufficient interest to report in some detail. It is greatly to be regretted that we had but a single opportunity to observe the individual for a few hours, as he left the city permanently the day after these observations were recorded.

Apart from the control of these ectopic rhythms occasionally seen following vagus stimulation either by direct pressure or reflexly as a result of various methods of clinical procedure, their voluntary control is seldom met with.

Although it is impossible in the present instance to determine with absolute exactness the means by which such voluntary inhibition is exercised, we have assumed that our use of the term "voluntary control" implies essentially the power on the part of the individual to bring about an abrupt change in his cardiac rate that is undoubtedly induced by some indirect vagal stimulation.

The subject of this note had for many years experienced attacks of abrupt, extreme acceleration of his cardiac rate, brought on at widely varying intervals by some unusual slight exertion, or often without any definitely known exciting cause, these attacks always being accompanied by the usual symptoms of distress referable to his disturbed circulation. Four or five years previously he first noticed that he had acquired the power to cut short these attacks, as he expressed it, by voluntary effort. This was accomplished apparently by a mental concentration associated frequently with an effort to yawn, or by a forced deep inspiration momentarily held.

When seen in September, 1917, by one of us, he seemed to have the power of initiating the onset of his tachycardia in much the same

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* From the Medical Clinic of the Cleveland City Hospital and the Western Reserve University

way that he now controls its offset, without any evident muscular effort. As, however, satisfactory records were not obtained at this time we cannot say definitely that this was a correct interpretation.

At present, February, 1918, he can induce the onset of his fast rhythm by various slight abrupt muscular efforts, but no similar effort had the slightest effect in controlling the offset of the new rhythm, this being accomplished solely by some conscious subjective effort while sitting quietly with his hands and foot in the immersion electrodes. Neither yawning nor any disturbance of his respiratory rhythm alone was sufficient to abort the attack, some other factor seeming to be necessary.

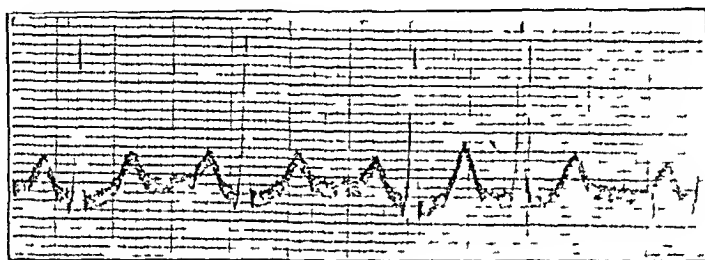


Fig 1—Normal electrocardiogram Lead II Rate 108 per minute The P-R interval measures 0.15 second Note the premature atrial systole

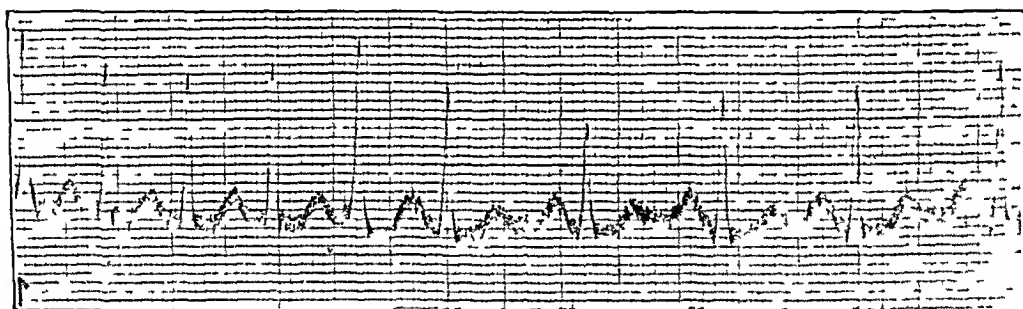


Fig 2—Lead II First half of the figure during the pathologic tachycardia, rate 200 per minute. At the point marked by the arrow he was asked to stop the paroxysm. The change from the fast to the slow rate is apparent, in this instance, without any long pause. The P-R interval measures 0.15 second. Note the marked inequality in the height of the R peaks, and with the onset of the slow rate the very suggestive "staircase" phenomenon.

His history is briefly as follows:

F P L,¹ aged 29, student, a Russian Jew. The family history was negative.

Personal History—There was no history of rheumatic fever, scarlet fever or diphtheria. He had an acute short attack of influenza in 1912, but no history of any other illness. He denied any venereal infection. He had used alcohol and tobacco in moderation. He thought smoking increased the frequency of the attacks and at one time stopped smoking for nine months, but noticed no material improvement.

¹ We are indebted to Dr. Harold Feil for the opportunity to observe this patient.

Present Illness—Occurrence of attacks of sudden acceleration of his heart rate dated from 1905, when 17 years of age. These attacks lasted from a few minutes to twelve hours, the longer ones always accompanied by a sense of fulness and distress in the head. These attacks commonly followed some unusual though slight muscular effort and were much more apt to occur if he missed his midday meal or at any time if he felt hungry.

Physical Examination—The man was of slight frame, fairly well nourished, muscular development slight, no pathologic deformities noted. The upper border of cardiac dulness was at the third interspace, the point of maximum impulse 10 cm from the midsternal line in the fifth interspace, right border at the right sternal edge, heart sounds clear, first sound at the apex slightly accentuated with every fourth or fifth systole, no murmurs heard, pulse apparently regular in rate and volume, though varying between the two slow rhythms 85 and 106 at different times. Blood pressure 112 and 80. The man gave one the impression of being a very high strung individual with an unstable nervous balance so characteristic of his race.

ANALYSIS OF THE ELECTROCARDIOGRAMS

In a detailed study of the figures accompanying this report, and additional similar records not reproduced, a number of interesting facts are apparent.

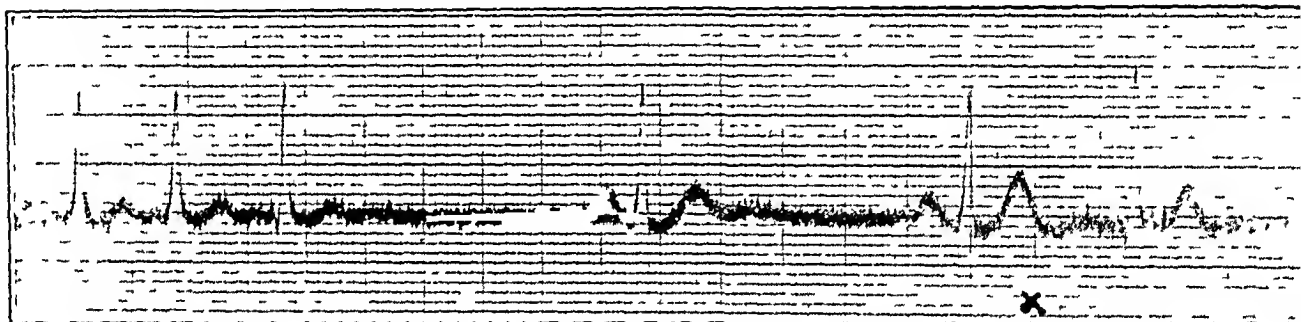


Fig 3—Lead II. Fast rate 200. At a point three cycles to the left of the first cycle of this figure he was asked to stop the tachycardia. Note the abrupt change to the slow rate. The last P-R interval before the first long pause is slightly increased. The R-R interval of the first long pause measures 1.20 seconds, the R-R interval of the second pause measures 1.04 seconds. The P-R interval with the long pauses measures 0.16 second, that with the premature systole at x measures 0.320 second.

The dominant rate of the pathologic rhythm remained constantly at approximately 200 per minute, varying between 196 and 204, a rate that, according to Lewis,² approaches the borderline in the arbitrary classification between a true paroxysmal tachycardia and atrial flutter. As a simpler and more logical distinction between these two forms of tachycardia, we have considered that the failure of ventricular response, in the presence of these borderline speeds, constituted the essential distinguishing difference, a distinction endorsed by Hart,³

² Lewis. Clinical Electrocardiography, Shaw & Sons, London, 1913.

³ Hart. Abnormalities of Myocardial Function, The Rebman Co., New York, 1917.

who further places the arbitrary difference in rate between the two at the still higher atrial speed of 250 per minute. In none of our records, however, was there at any time a failure of ventricular response during the presence of the atrial tachycardia.

THE VENTRICULAR COMPLEX

At times, but only for short intervals, the cardiac rate slowed down to 85 per minute, the dominant slow rate ranging between 106 and 108, with a normal electrocardiogram in all three leads and with a normal conduction time. The form of the ventricular complex remains the same at all speeds of the heart before, during and after atropin, showing no pathologic alteration except the alternation noted later.

In the presence of the pathologic tachycardia it is possible that confusion might arise in an analysis of the galvanometric curves as to the presence of a negative P-wave with a lengthened conduction time, were the evidence always as suggestive as is seen in the distinctly negative deflection of the string following R in Figure 9. Elsewhere

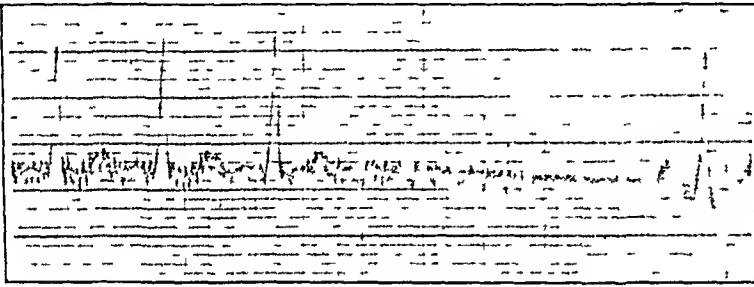


Fig 4—Lead II. Abrupt stoppage of the fast rate. Signal given four cycles to the left of the first cycle of the figure. R-R interval measures 1.42 seconds.

in all our records there was no such suggestive negative deflection, and we have assumed that T and P are fused, P appearing as a positive wave, as is so evident with the occurrence of isolated premature atrial contractions.

In all the records of our series there is a conspicuous variation in the height of the R peaks, amounting in many instances to a definite alternation. In Figure 2, illustrating the first recorded transition from the fast to the slow rate, the first four cycles of the slow rhythm show a very suggestive "staircase" phenomenon, which may be looked on as additional evidence of a vagus reflex.⁴

THE P-R INTERVAL

With the onset of the fast rhythm the P-R interval remains practically unchanged. With the abrupt offset of the pathologic tachy-

⁴ Vinis: *Heart*, 1912, 4, No 2, p 123. Ritchie: *Quart Jour Med*, 1912, 6, No 21, p 47.

cardia to the slower rate of 106 following voluntary effort, there is but a slight change in the conduction time preceding the transition, the P-R interval lengthening for the last cycle of the fast rate to shorten again with the establishment of the slower rhythm after the pause.

When, however, he was able to slow the dominant rate of 106 down to 85 per minute, the transition was invariably accompanied by a conspicuous lengthening of the P-R interval, associated with an isolated extrasystole of atrial origin, followed by a long pause (Fig 8). At x (Fig 8) the P-R interval measures 0.28 sec. In another similar instance it was increased to 0.30 sec.

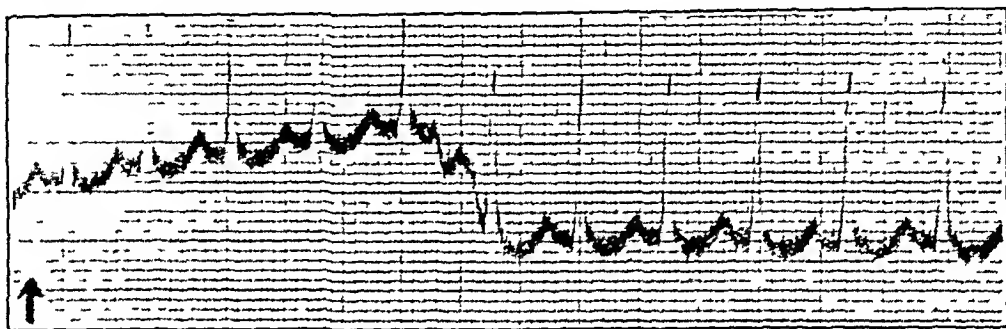


Fig 5—Lead II Rate 200 Right vagus stimulation during the tachycardia. Vagus pressure applied at point marked by arrow. No change in rate.

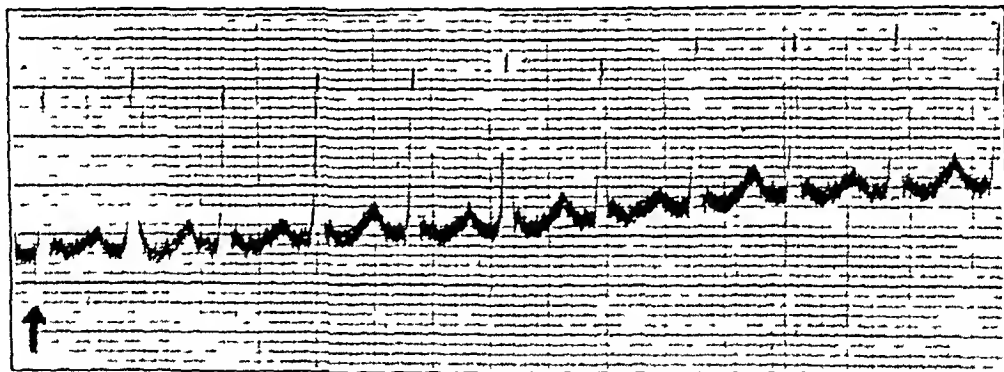


Fig 6—Lead II Rate 200 Left vagus stimulation during the tachycardia. Vagus pressure applied at the point marked by arrow. No change in rate.

The P-R interval then measures 0.16 sec during the slowest rate of 85, the dominant slow rate of 106, in the presence of the pathologic cardia to the slower rate of 106 following voluntary effort, there is tachycardia and in the escape under atropin, only lengthening conspicuously, as is to be expected, with the transition from a fast to a slower rate.

EFFECT OF MECHANICAL VAGUS STIMULATION

Repeated attempts by pressure applied over both the right and left vagus failed utterly to induce the slightest change in either the rate or the cardiac rhythm. This failure to demonstrate any alteration in the cardiac response to mechanical stimulation of the vagi seems

curiously inconsistent with the results that one would have expected in an instance of the sort under consideration. That in many instances of paroxysmal tachycardia vagal stimulation is without the slightest effect is too well known to need comment, but just how to reconcile the man's own power of subjective control over his fast rhythm, so evidently of vagal origin, in the face of our failure to influence it in the slightest by vagal pressure, is not so simple.

Cohn and Fraser,⁵ in a study of paroxysmal tachycardia and the effect of vagus pressure, suggest that when vagal stimulation by pressure fails to control the paroxysmal attack and other methods succeed, the results may well be attributed to the stimulation of the inhibitory mechanism by the successful procedure and failure to do so by all other methods, an explanation that is after all not wholly satisfactory.

In a study of certain cases of rhythmic irregularities Robinson and Draper⁶ regarded the inability to produce any change in the

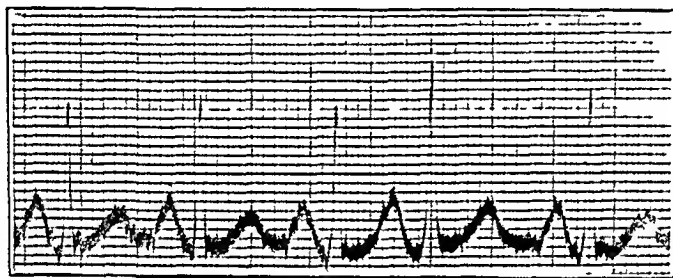


Fig 7—Lead II Twenty-five minutes after 13 mg of atropin Rate 144 per minute Fifteen minutes after atropin, rate 135, an hour after atropin, rate 120 Two hours after atropin the heart had escaped from atropin effect Note the alternation

cardiac rhythm by vagal pressure as due to an increased vagal tone, the heart in one case described by them escaping under atropin and attaining a rate greatly in excess of the rhythmic tachycardia, when the individual was no longer able to induce the changes in rhythm brought about by deep forced inspiration. They conclude that in this case the vagus tone "controlled a heart which would otherwise have beat at an abnormally rapid rate."

In this connection the experimental observations of Rothberger and Winterberg⁷ on the influence of the vagus and accelerator nerves on the galvanometric curves from the dog's heart are of interest. These observers were able to show that in the experimental animal stimulation of the vagus and accelerator yielded curves essentially the

⁵ Cohn and Fraser *Heart*, 1913, 5, No 1, p 93

⁶ Robinson and Draper *Heart*, 1912, 4, p 97

⁷ Rothberger and Winterberg *Centralbl f Physiol*, 1910, 24, 790 *idem*, *Pflüger's Arch f d ges Physiol*, 1910, 135, 506

antithesis of each other, vagus stimulation giving a low voltage P and T with a conspicuous R deflection, while stimulation of the sympathetic gave a lower R with conspicuous P and T waves. There are admittedly many difficulties in applying the experimental evidence in this connection too dogmatically to the clinical picture, and yet in those instances in which the cardio-inhibitory or accelerator influence is definitely subject to marked voluntary control the suggestive comparison of the experimental and clinical galvanometric curves should not be lost sight of.

Flavell and White,⁸ in reporting a case of voluntary acceleration of the cardiac rate not associated with any apparent change of the pacemaker, referring to the observations of Lewis and Cotton⁹ say that "the changes in the electrocardiographic deflections during the acceleration are those which are known to occur when the sympathetic is stimulated experimentally." Further, as evidence that the voluntary increase of the heart rate is the result, in great part at least, of the

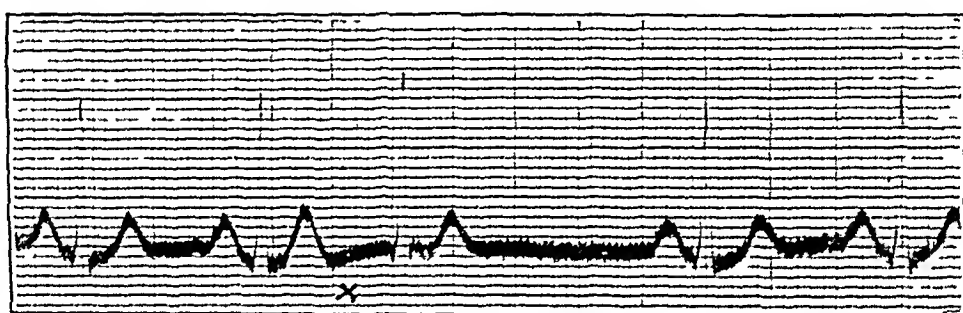


Fig 8—Lead II After escape from atropin effect. Note the voluntary control of the slow rate. First half of figure, rate 108, second half following the long pause, 86 per minute. The P-R interval measures 0.16 second for the first three cycles. With the extrasystole at x the P-R interval measures 0.26 second. The R-R interval following the extrasystole measures 0.96 second. The P-R interval of the next cycle measures 0.14 second and then reverts to 0.16 second.

action of the accelerator mechanism, they cite the fact that "the escape under atropin in large doses produces not one-half of the increase in pulse rate that results from voluntary acceleration." A fact, however, of even greater significance, it seems to us, in the case reported by Flavell and White, is the ability on the part of the subject of their note to break through the rate under the escape from atropin and induce a higher rate, an ability not possessed by the subject of this report.

In discussing this question as to why stimulation of the vagi by pressure is effectual in some cases of paroxysmal tachycardia and not

⁸ Flavell and White. *Heart*, 1917, 6, No. 3, p. 175.

⁹ Lewis and Cotton. *Proc. Phys. Soc.*, June 28, 1913.

¹⁰ Robinson G. C. *THE ARCHIVES INT. MED.*, 1915, 16, 967.

in others, Robinson¹⁰ says that it seems probable that this difference is due to the character of the cardiac derangement responsible for the tachycardia, depending on the anatomic relation between the distribution of the vagi and the point taking up the rôle of hyperactive pacemaker. This conclusion, so readily applicable in many instances, does not, however, aid in the explanation of the failure of vagal pressure to control the fast rate in our case, which seems so curiously paradoxical.

ESCAPE UNDER ATROPIN

Following 1.3 mg of atropin the ventricular escape reached as its highest rate, 144 per minute (Fig 7). The degree of ventricular escape amounted to approximately the average normal figure, being on the basis of the dominant rate, an increase of 35 per cent.

We have not assumed that the mere removal of vagal control in this instance would *per se* tend to increase the incidence of the paroxysmal attacks, but because of the very evident subjective control over the pathologic tachycardia, and in spite of the fact that it was constantly so uniformly rapid, we hoped that under the influence of atropin it might be possible to induce the pathologic rhythm with even greater facility than before its administration. While under the influence of atropin, however, he was utterly unable to break through the rate due to the cardiac escape and induce the higher speed of the ectopic rhythm. That all inhibitory vagal control had been removed was evidenced by the utter failure to control subjectively the rate under atropin, and by the conspicuous physiologic effects of the drug. Had the pathologic tachycardia been of a lower rate than that under the escape following atropin, the explanation for the failure to induce the ectopic rhythm after removal of vagal tone would be less difficult. That, however, the administration of atropin or belladonna in some form over a variable period of time to persons subject to attacks of paroxysmal tachycardia does not increase the incidence of such attacks is also a matter of observation.

The reaction to atropin in this case is further proof that we were not dealing with an ectopic focus wholly removed from neurogenic control as in the high speed atrial rate of true flutter. Following partial recovery from the atropin effect, two hours after its administration, he was again able to induce the pathologic rhythm and could again retard his slow rate of 106 down to 85 per minute (Figs 8 and 9).

THE INCIDENCE OF PREMATURE CONTRACTIONS

As is to be expected, the incidence of single premature atrial contractions increased with the slower rates, disappearing entirely in the presence of the tachycardia. But of greater interest is the fact that

they do not disappear entirely under atropin, evidence, we consider, of definite pathologic significance. When these occur, as in Figure 1, free from any conscious effort on the part of the individual to slow his heart, the atrial pause is less than compensatory by 0.16 sec. Under the influence of conscious effort to slow the cardiac rate, as in Figure 8, the atrial pause is greatly increased, being overcompensated by 0.26 sec. There is, further, a curiously constant relationship in the time of the appearance of the atrial extrasystole to the preceding ventricular complex. Extra systoles of ventricular origin were at no time recorded.

VOLUNTARY CONTROL OF THE TACHYCARDIA

In every instance when asked to stop the pathologic tachycardia the result was accomplished within a few cycles of the command, and in every record but one (Fig. 2) the transition occurred with one or more long pauses during which the R-R interval measures all the way from 0.96 sec. to 1.42 sec. The pause involved a complete standstill of the

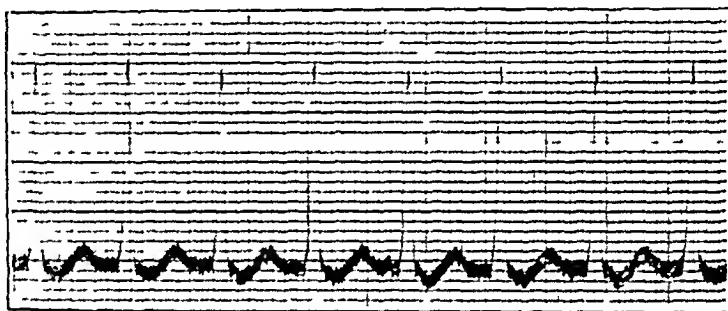


Fig. 9—Lead II. Rate 200. After the escape from atropin effect. The pathologic tachycardia. Note the alternation and the very suggestive negativity of the string following the R-complex. See reference in text.

heart and frequently measured more than twice the R-R interval of the dominant rhythm of 106 to the minute. In Figure 4 it exceeds even twice the R-R interval of the slowest rate of 86 to the minute. This fact, together with the lengthening of the P-R interval that invariably accompanied isolated premature systoles, points to the predominant effect of vagus control in cutting short the fast rhythm and in slowing down the predominant slow rate of 106 to 85. That the abeyance of vagus control had not the slightest influence in inducing the paroxysmal rhythm seems as equally well established as is the evidence of the man's voluntary control over his inhibitory mechanism.

When asked to cut short the paroxysmal attack while connected with the galvanometer it was interesting to watch his method of procedure. He closed his eyes, inclined his head backward and slightly to the left and then would apparently concentrate his mind on the effort to check the tachycardia without any visible change in the respiratory rate.

SUMMARY

In view of the constant similarity of the ventricular complex, the constancy of the conduction time, except during the transition from a higher to a lower rate, together with the constant time relationship of the extrasystoles to the preceding ventricular contraction and the direction of the P-wave, we have assumed that we were dealing with an ectopic rhythm originating in the upper level of the atrium near the pacemaker, conspicuously under the control of subjective inhibitory reflexes, but utterly uninfluenced by vagal stimulation

There is no demonstrable evidence of any accelerator influence or control over the tachycardia, in spite of the general inferences supporting such a view and the similarity of the ventricular complexes to the experimental observations alluded to

REMARKS ON THE CONCENTRATION OF UREA IN HUMAN BLOOD

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The majority of investigators who have studied the problem of kidney function, particularly in relation to impaired elimination, accord increasing importance to the estimation of nitrogenous substances in the blood. Though the relation of nitrogen retention in the blood to the pre-uremic and uremic manifestations in the clinical picture of nephritis is not sufficiently understood to allow definite interpretation as to diagnosis and prognosis, there can be no doubt that nitrogen retention is intricately connected with disturbances arising from impaired kidney function.

Among the nitrogenous substances of the blood, urea has received particular attention for a number of reasons which need not be analyzed here. As a result of many careful investigations, the retention of urea in the blood is now generally regarded as a reliable diagnostic sign of faulty kidney function, but, on the other hand, there still remains a disturbing degree of confusion as to what should be considered the normal and what a pathologic urea content of the blood.

The concentration of urea in the blood of healthy adults has been the subject of numerous investigations, the more important of which are summarized in Table 1.

Of the investigators listed here, Folin and Denis,¹ Tileston and Comfort,² and Myers and Killian,³ all find practically the same narrow range of normal values. On the other hand, McLean and Selling,⁴ Gettler and Baker,⁵ and Addis and Watanabe,⁶ find a very much wider range of normal values, and Schwartz and M'Gill⁷ are unique in that the highest value in their series of normals is practically identical with the low limit of the normal range as determined by other investigators. This fact seems to have been overlooked by other workers, for Schwartz and M'Gill are frequently quoted as finding from 10.8 to 25.2 mg of urea nitrogen per 100 c.c. of blood, whereas they actually

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1 Folin, O., and Denis, W. *Jour Biol Chem*, 1913, **14**, 29.

2 Tileston, W., and Comfort, C. W. *THE ARCHIVES INT MED*, 1914, **14**, 620.

3 Myers, V. C., and Killian, J. A. *Jour Biol Chem*, 1917, **29**, 179.

4 McLean, F. C., and Selling, L. *Jour Biol Chem*, 1914, **19**, 31.

5 Gettler, A. O., and Baker, W. *Jour Biol Chem*, 1916, **25**, 211.

6 Addis, T., and Watanabe, G. *THE ARCHIVES INT MED*, 1917, **19**, 507.

7 Schwartz, H., and M'Gill, C. *THE ARCHIVES INT MED*, 1916, **17**, 42.

report 10.8 to 25.2 mg of urea per 100 c c of blood. Moreover, these extremely low figures are reported as the urea content of specimens taken "two and one-half hours after a heavy protein meal," a time when the urea concentration of the blood would naturally be somewhat increased as a result of the processes of absorption and assimilation. On the whole, the evidence for a wide range of normal values is far from convincing, the concentration of urea nitrogen in the blood of normal, healthy adults seems to lie between 12 and 15 mg per 100 c c.

TABLE 1—CONCENTRATION OF UREA NITROGEN IN NORMAL HUMAN BLOOD

Investigators	Number of Subjects	Urea N of Blood, Mg per 100 C c	Remarks
Folin and Denis ¹	16	11 to 13	Three to six hours after breakfast
Schwartz and M'Gill ²	4	5 to 7.1	After seventeen hours' fast
Schwartz and M'Gill ²	15	5 to 11.7	Two and one-half hours after a "heavy protein meal"
Addis and Watanabe ³	22	10.5 to 28	Before breakfast, 106 determinations on twenty-two subjects
Gettler and Baker ⁵	30	15 to 25	Three hours after a standard breakfast
Tileston and Comfort ²	5	12 to 14.1	After twelve hours' fast
Tileston and Comfort ²		13.1 to 20.9	Two and one-half hours after an average meal
Myers and Killian ³	6	12 to 15	Before breakfast
McLean and Selling ⁴		10 to 23	Under varying conditions

Assuming the accuracy of these narrow limits as repeatedly confirmed by the observations of Folin and his collaborators, and of various workers in our own laboratories, we are still confronted with the question, Is the normal concentration of urea in the blood of hospital patients without evidence of kidney lesion the same as that of healthy individuals, and is the normal sharply differentiated from the pathologic?

In the hope of answering these questions we have made the following study of 298 routine analyses of the blood of 244 patients treated in our own medical wards. This special series was selected for investigation because it includes the analysis of at least one specimen from each patient in the wards during a period of five months, and for that reason seems to offer a fairer criterion of urea values than would a study of carefully selected groups of typical cases. All specimens examined in which the urea nitrogen exceeded 35 mg per 100 c c, were from patients unquestionably nephritic, for this reason the series discussed here includes only those cases in which the urea nitrogen was less than 35 mg per 100 c c.

In order to obtain specimens of which the urea content is justly comparable, two variable factors must be guarded against (1) during

the processes of digestion and absorption, the increase in concentration of blood urea depends partly on the nature of the food intake, and (2) this increase is of a more lasting nature in persons with impaired renal excretory powers than in healthy persons. We have, therefore, adopted the practice of taking all blood specimens before

TABLE 2—CASES WITH UREA NITROGEN OF LESS THAN
12 MG PER 100 Cc OF BLOOD

Case	Age	Sex	Urea N of Blood, Mg per 100 Cc	Diagnosis	Remarks
1 J C	50	♀	10.8	Duodenal ulcer	
2 A G	12	♀	10.5	Duodenal ulcer	
3 D T	30	♂	10.8	Gastric ulcer	
4 M C	55	♀	11.6	Typhoid	
5 B G	21	♀	10.8	Typhoid	Occasional cast
6 E P	23	♀	11.6	Spastic colitis, adhesions	
7 R K	23	♀	10.1	Spastic colitis	
8 H D	21	♂	11.6	Chronic endocarditis	
9 J L	19	♀	11.1	Chronic endocarditis, myocarditis	Faint trace of albumin
10 G G	55	♂	11.6	Chronic endocarditis	
11 M B	30	♂	11.6	Huntington's chorea	
12 P K	25	♀	11.6	Neurasthenia	
13 S W	60	♂	11.1	Pyloric obstruction, duodenal ulcer	
14 T M	23	♂	11.1	Chronic constipation	Phthalein, 19 per cent
15 N F	45	♀	11.1	Chronic constipation, colitis	
16 V F	34	♂	10.8	Auricular fibrillation	Faint trace of albumin
17 N F	65	♀	10.8	Diabetes mellitus	Occasional cast
18 V S	18	♂	11.6	Meningitis	
19 J H	20	♂	10.8	Lobar pneumonia	
20 M C	22	♀	9.8	Undeveloped, retro verted uterus	Phthalein, 30 per cent, 34 per cent
21 J E	54	♀	11.6	Calloused ulcer of pylorus	
22 J W	51	♂	11.6	Retroperitoneal sarcoma	Phthalein, 26 per cent
23 R K	36	♀	9.0	Chronic endocarditis, auricular fibrillation	
24 J S	38	♂	10.5	Hypertension, throm bosis of central vein of left eye	Blood pressure, 165/100
25 F S	35	♀	11.1	Enteroptosis	Phthalein, 36 per cent
26 M B	39	♀	11.1	Enteroptosis	
27 I G	50	♂	10.8	Chronic parenchyma tous nephritis	Trace of albumin
28 S R	29	♀	11.6	Parenchymatous ne phritis, hemorrhagic	Moderate amount of albu min, occasional cast
29 S F	35	♀	11.1	Gastritis and gastralgia	
30 M B	35	♀	10.5	Carcinoma of sigmoid and liver	
31 C R	24	♀	11.1	Lymphosarcoma	

TABLE 3—CASES WITH UREA NITROGEN OF 12.1-15 MG PFR 100 Cc OF BLOOD

Case	Age	Sex	Urea N of Blood, Mg per 100 Cc	Diagnosis	Remarks
32 H C	24	♂	13.5	Lobar pneumonia	Blood sugar, 0.171 per cent
33 C E	29	♂	13.5	Lobar pneumonia	Blood sugar, 0.168 per cent
34 D B	16	♀	12.6	Lobar pneumonia	
35 N S	24	♂	13.0	Lobar pneumonia	Blood sugar, 0.177 per cent
36 M W	25	♀	13.5 13.0	Bronchial pneumonia	
37 Y B	19	♀	13.5	Pleurisy, pneumonia	
38 M G	25	♀	12.6 9.3	Pleurisy, with effusion	Phthalein, 22 per cent
39 D R	30	♂	14.1	Pleurisy	Faint trace of albumin
40 C J	31	♂	12.6	Chronic gout	Creatinin, 3.5 mg per 100 cc
41 H S	31	♂	14.5	Gas poisoning	
42 G H	68	♂	14.5 13.5	Chronic arthritis	
43 A W	10	♀	12.3	Chronic arthritis	
44 H M	41	♀	12.6	Chronic arthritis	
45 A B	52	♂	14.5	Chronic arthritis	Blood pressure 170/100
46 E T	45	♀	12.0	Acute septic arthritis	
47 L S	27	♀	12.3	Pulmonary tuberculosis	
48 E K	42	♀	12.0	Pulmonary tuberculosis	Phthalein, 34 per cent, blood pressure, 215/115, faint trace of albumin
49 J S	18	♂	13.0	Incipient tuberculosis	Moderate number of casts
50 M G	30	♀	13.8	Incipient tuberculosis	
51 J F	17	♂	13.7	Tuberculosis of left kidney	Trace of albumin
52 A A	49	♀	12.0	Tuberculosis, keratitis	
53 A B	41	♂	12.6	Aortitis	
54 H K	10	♂	12.6	Spastic colitis	Occasional cast
55 M M	58	♂	12.6	Spastic colitis	Phthalein, 10, 24, 17 per cent
56 J S	28	♂	14.1	Spastic colitis	
57 B L	40	♀	14.1	Myocarditis	Blood sugar, 0.177 per cent, faint trace of albumin, phthalein, 32 per cent, blood pressure, 155/125
58 J V	33	♂	13.8	Myocarditis	
59 T C	51	♂	13.1	Myocarditis	Occasional cast
60 B G	47	♀	12.6	Myocarditis	
61 E B	44	♂	12.5	Myocarditis	
62 L R	61	♀	13.8	Hysteria	
63 R M	14	♂	14.8	Tetanus	
64 M D	23	♀	12.6	Arteriosclerosis, hypertension	Trace of albumin
65 M Y	66	♂	13.6	Arteriosclerosis, aortitis	Moderate amount of albumin, phthalein, 29 per cent
66 C H	44	♂	12.6	Lues, general paresis	
67 L N	36	♀	14.1	Lues	Faint trace of albumin
68 G L	50	♂	14.5	Paresis	

TABLE 3—CASES WITH UREA NITROGEN OF 12.1-15 MG PER 100 CC OF BLOOD—(Continued)

Case	Age	Sex	Urea N of Blood, Mg per 100 C c	Diagnosis	Remarks
69 F B	35	♂	12.8	Paresis	Phthalein, 27 per cent
70 S M	28	♂	13.5	Syphilis, progressive muscular atrophy	
71 G R	24	♀	13.5	Typhoid	
72 L G	13	♀	12.3	Typhoid	
73 B B	23	♀	12.6	Gastric ulcer	
74 H M	44	♂	12.6	Gastric ulcer	
75 J K	36	♂	12.3	Gastritis	
76 J H	62	♂	13.3	Carcinoma of stomach	Trace of albumin, moderate number casts, creatinin 3.5
77 M P	32	♀	12.3	Autointoxication	
78 M S	23	♂	12.3	Psychasthenia	Occasional cast, faint trace of albumin
79 Y F	33	♀	13.0	Subacute gastro-enteritis	Creatinin, 3.5 mg per 100 c c
80 J V	31	♂	13.8	Pontine neoplasm	
81 L S	13	♂	13.0	Malaria	
82 Y S	21	♀	13.8	Atrophy of eyeball	
83 L L	8	♂	12.6	Tonsillitis	
84 B H	32	♀	13.0	Pyorrhea, leukorrhea	
85 L Z	21	♀	14.5	Hysterical epilepsy	Faint trace of albumin
86 C M	55	♂	13.0	Atrophic cirrhosis of liver, ascites, pleural effusion	
87 A F	27	♂	12.6	Hypertrophic cirrhosis of liver	
88 M F	50	♀	14.5	Abdominal tumor of spleen, syphilis	
89 H B	38	♀	14.1	Chronic hypertension, neurasthenia	
90 H O	25	♀	13.5	Spinal lesions	
91 E M	27	♂	14.8	Streptococcus septicemia, chronic endocarditis	
92 D T	55	♂	14.8	Chronic appendicitis	Occasional cast
93 S C	48	♂	14.5	Chronic appendicitis	
94 F L	29	♀	14.5	Chronic constipation and appendicitis	
95 M H	43	♂	14.8	Pulmonary abscess	
96 A C	54	♀	12.0	Chronic endocarditis, general carcinoma-tosis	
97 M B	52	♀	14.8	Endocarditis	Blood sugar, 0.192 per cent
98 G T	31	♀	13.5	Endocarditis	
99 D M	19	♂	12.6	Malignant endo-carditis	
100 O B	18	♂	14.5	Chronic endocarditis, mitral regurgitation and stenosis	
101 F G	63	♀	12.0	Diabetes mellitus	Occasional cast, blood sugar, 0.163 per cent
102 I G	60	♀	14.0	Diabetes mellitus	

TABLE 3—CASES WITH UREA NITROGEN OF 12.1-15 MG
PER 100 Cc OF BLOOD—(Continued)

Case	Age	Sex	Urea N of Blood, Mg per 100 Cc	Diagnosis	Remarks
103 W P	43	♂	13.5	Diabetes mellitus	Blood sugar, 0.228 per cent
104 R V	19	♀	15.0	Diabetes mellitus	
105 J M	56	♂	13.5	Diabetes eareinoma of liver	Blood sugar, 0.280 per cent
106 A L	34	♀	13.0	Chronic endometritis and appendicitis	
107 H S	46	♂	13.5	Neuritis	
108 J C	65	♂	12.0	General eareinoma tosis	Phthalein, 29 per cent
109 C M	41	♀	12.3	Gastroptosis	
110 G R	44	♀	13.5	Hanot's disease	
111 D T	37	♀	11.6 12.5	Splanchnoptosis	
112 D	38	♀	11.1 13.1	Splenomegaly	
113 C	75	♂	13.5 13.8 12.8	Myositis	Occasional cast
114 F C	52	♂	13.0	Adhesions, peri duodenal	
115 M B	31	♀	14.1	Adhesions, duodenal	Blood pressure, 160/120
116 R A	23	♀	14.8	Adhesions, gallblad der periduodenal	
117 M G	36	♀	13.5	Cholecystitis	
118 C C	50	♀	14.1	Cholecystitis, chronic pancreatitis	
119 R S	32	♀	13.5	Pyelitis, left	Trace of albumin
120 V O	44	♂	12.6	Hemiplegia	Trace of albumin
121 S S	34	♀	14.1	Enteroptosis, renal ciculus	Phthalein, 38 per cent
122 B B	30	♀	12.3	Bronchial asthma	Occasional cast
123 F P	43	♂	12.0 10.8 11.1 11.6	Asthma, chronic endo carditis, chronic parenchymatous nephritis	Large amount of albumin moderate number of casts
124 F P	38	♂	13.0 9.8	Ineipient interstitial nephritis	Phthalein, 31 per cent
125 C B	56	♂	14.6 12.0	Chronic interstitial nephritis	Blood sugar, 0.222 per cent, 0.183 per cent, moderate amount of albumin, many casts phthalein, 22 per cent, blood pressure, 155/85
126 R G	45	♀	13.5 9.9 13.0	Chronic interstitial nephritis, low sugar tolerance	Blood sugar, 0.22 per cent 0.172 per cent, 0.177 per cent, faint trace of albu min, moderate number of casts
127 T W	12	♂	14.6	Sydenham's chorea, hypertrophy of ton sils and adenoids	
128 L G	41	♀	13.0	Spasmodic stricture of cardiac urea of stomach	
129 F S	6	♂	13.8	Colitis	
130 A S	22	♂	14.8	Flatfoot, partial at rophy of peri articu lar surfaces of ankle joints	

breakfast, while the patient is still in a fasting condition, in order to obtain specimens of which the urea values are truer indicators of kidney function than would be the case if the specimens were taken while absorption is in process

TABLE 4—CASES WITH UREA NITROGEN OF 15.1 TO 18 MG PER 100 CC OF BLOOD

Case	Age	Sex	Urea N of Blood, Mg per 100 Cc	Diagnosis	Remarks
121 J D	21	♂	15.8	Perinephritic abscess	Occasional cast
122 M R	44	♀	15.8	Chronic appendicitis	
123 R P	43	♂	16.5	Chronic appendicitis, duodenal ulcer	
124 V D	35	♂	12.9	Chronic appendicitis, spastic colitis	Creatinin, 3.8, 3.4 mg per 100 cc Moderate number of casts
125 J C	44	♂	14.5	Duodenal ulcer	
126 J C	31	♂	17.0	Duodenal ulcer, chronic vesiculitis	
127 S P	39	♂	16.1	Duodenal ulcer	
128 S K	52	♂	15.4	Duodenal ulcer	
129 A K	31	♂	16.6	Duodenal ulcer, adhesions	
130 M S	24	♀	17.3	Gastric ulcer	
131 M S	56	♀	16.1	Gastric ulcer	
132 M L	48	♀	15.8	Gastric cancer	
133 M D	54	♀	18.0	Gastroptosis	
134 T C	58	♂	16.1	Chronic gastritis, alcoholic	
135 M S	47	♀	17.0	Periduodenal adhesions	
136 W M	56	♂	17.1	Periduodenal adhesions	Occasional cast
137 R Z	66	♀	17.6	Carcinoma of duodenum	
138 G B	47	♂	16.3	General carcinoma of abdomen	
139 B B	39	♂	16.1	Partial pyloric obstruction	Phthalein, 36 per cent
140 A T	24	♀	18.0	Interoptosis	
141 S G	23	♂	15.5	Interoptosis, typhilitis	
142 L B	63	♂	17.3	Myocarditis	Trace of albumin
143 A M	57	♂	17.3	Myocarditis	
144 A W	26	♂	18.0	Congenital syphilis	
145 G G	31	♂	17.6	Syphilis, chronic	Creatinin, 3.5 mg per 100 cc
146 S K	63	♂	15.6	Appendicitis	
147 A D	49	♂	18.0	Syphilis	
148 A D	49	♂	16.2	Syphilis, adhesions, bronchial asthma	Phthalein, 12 per cent, faint trace of albumin, moderate number of casts Phthalein, 26 per cent
149 T D	46	♂	16.5	Hemiplegia, syphilis	
150 C A	60	♀	17.0	Septic arthritis	
151 J G	72	♂	16.0	Scleritis	Creatinin, 4.3 mg per 100 cc
152 H U	28	♂	15.8	Hemorrhoids	
153 J G	72	♂	15.9	Typhoid	
154 D M	26	♂	15.5	Perineal abscess	Phthalein, 20 per cent
155 C M	27	♂	15.5	Auricular fibrillation	
156 M S	12	♂	16.5	Purpura simplex	
157 W W	23	♂	16.1	Amyotrophic lateral sclerosis	Phthalein, 24 per cent, 29 per cent Moderate number of casts
158 F J	66	♀	16.1	Osteoarthritis	
159 T P	22	♂	16.1	Brain tumor	
160 A M	46	♂	17.8	Chronic endocarditis	Trace of albumin, occasional cast
161 F M	55	♀	17.8	Chronic endocarditis	
162 W I	19	♂	17.0	Endocarditis	
163 I L	27	♂	15.8	Endocarditis mitral stenosis	Occasional cast
164 K R	67	♀	16.5	Chorea endocarditis	
165 L P	14	♀	17.3	Chorea, endocarditis	
166 I Z	37	♂	17.0	Acrophagy	

TABLE 4—CASES WITH UREA NITROGEN OF 15.1 TO 18 MG PER 100 C c OF BLOOD—(Continued)

Case	Age	Sex	Urea N of Blood, Mg per 100 C c	Diagnosis	Remarks
176 S B	15	♂	16.1 9.3	Diabetes mellitus	Phthalein, 30 per cent, blood sugar, 0.336 per cent, creatinin, 3.6 mg per 100 c c
177 M J	57	♂	12.6 16.1	Diabetes mellitus	Blood sugar, 0.300 per cent, 0.188 per cent, occasional cast
178 A N	48	♂	16.1	Acute gangrenous appendicitis	Occasional cast, blood sugar, 0.261 per cent
179 A R	26	♂	15.5	Cecal stasis, chronic appendicitis	
180 S S	56	♂	16.5	Hemiparesis, motor aphasia	
181 M A	22	♀	18.0 13.8	Cholelithiasis	
182 T L	37	♂	16.0	Internal hemorrhoids	
183 F K	40	♂	16.0	Cecal stasis	
184 A B	22	♀	15.1	Bronchial asthma	
185 H R	33	♂	17.5 12.6	Hernia	Faint trace of albumin
186 M K	31	♀	16.3 18.0	Lobar pneumonia	Faint trace of albumin
187 L S	55	♂	17.8	Arteriosclerosis	Occasional cast, blood pressure, 210/115, 205/160
188 R S	57	♀	16.5	Aneurism of aortic arch	Blood sugar, 0.196 per cent, trace of albumin, occasional cast, blood pressure, 228/112
189 R S	50	♂	16.5	Tabes dorsalis	
190 P F	18	♂	18.0	Pulmonary tuberculosis	

TABLE 5—CASES WITH UREA NITROGEN OF 18.1 TO 20 MG PER 100 C c OF BLOOD

Case	Age	Sex	Urea N of Blood, Mg per 100 C c	Diagnosis	Remarks
191 H B	36	♂	18.6	General carcinomatosis	Occasional cast
192 N B	41	♂	19.0	General carcinomatosis	
193 F D	53	♂	19.5	Carcinoma of stomach	
194 E L	51	♂	18.6	Duodenal ulcer	
195 F S	28	♂	18.3	Duodenal ulcer	
196 T D	43	♂	19.0	Gastric or duodenal ulcer	
197 A A	39	♂	18.5	Interoptosis, post pyloric ulcer	Creatinin, 3.6 mg per 100 c c
198 J M	43	♂	18.3	Aneurism of aorta	Moderate amount of albumin, casts
199 W J	45	♂	19.0	Aortitis, arteriosclerosis	Occasional cast, blood pressure, 205/130
200 M F	34	♀	19.0	Hemiplegia	Phthalein, 30 per cent
201 H F	16	♂	18.3	Typhoid	
202 A B	62	♀	19.0	Lues, chronic ulcers of leg	
203 J V	13	♀	18.3	Chronic parenchymatous nephritis	Trace of albumin, moderate number of casts
204 N A	54	♂	19.0 14.7	Chronic endocarditis	Faint trace of albumin, phthalein, 29 per cent
205 H O	60	♀	16.1 19.3	Diabetes	Blood sugar, 0.244 per cent, 0.200 per cent, occasional cast
206 F J	66	♂	18.6	Diabetes mellitus, syphilis, chronic nephritis	Blood sugar 0.372 per cent, phthalein, 32 per cent, trace of albumin, many casts

TABLE 6—CASES WITH UREA NITROGEN OF 20.1 TO 25 MG PER 100 Cc OF BLOOD

Case	Age	Sex	Urea N of Blood, Mg per 100 C c	Diagnosis	Remarks
207 M K	47	♂	23.1	Gastric ulcer	Phthalein, 27 per cent, creatinin, 3.8 mg per 100 c c
208 J Z	22	♀	22.5	Gastric ulcer, marked secondary anemia	
209 A R	38	♂	21.1	Duodenal ulcer	Occasional cast, creatinin, 3.5 mg per 100 c c
210 L W	41	♂	21.7	Carcinoma of pylorus	Blood sugar, 0.168 per cent, phthalein, 33 per cent
211 M F	25	♀	23.0	Spastic colitis	
212 M D	35	♂	14.5	Pulmonary tuber- culosis	
213 M A	44	♂	22.2	Anterior medio- sternal tumor	Moderate number of casts
214 S	58	♂	20.5	Hemorrhagic retinitis	
215 J P	56	♂	22.1	Syphilitic aortitis	Phthalein, 28 per cent
216 J L	62	♂	22.2 17.0	Renal hemorrhage, arteriosclerosis, myocarditis	Blood pressure, 195/110, 205/110
217 A D	44	♂	20.7 18.6 15.5	Hypopituitarism	Faint trace of albumin, occa- sional cast
218 M L	65	♂	22.7	Myocarditis	
219 J A	51	♂	21.8	Myocarditis	Phthalein, 26 per cent
220 E H	56	♀	22.5 14.8	Myocarditis	Trace of albumin, blood pres- sure, 190/110, 162/102
221 J C	47	♂	20.7 12.0	Myocarditis, hyper- tension, chronic parenchymatous nephritis	Trace of albumin, moderate number of casts
222 J H	44	♂	25.0	Chronic myocarditis	Occasional cast
223 L F	31	♂	21.1	Interstitial hepatitis, jaundice	Faint trace of albumin, many casts
224 R B	60	♂	23.7	Cholelithiasis, renal calculi	
225 S S	35	♂	20.8	Chronic endocarditis, mitral regurgitation, mitral stenosis	Blood sugar, 0.168 per cent, phthalein, 6 per cent, 20 per cent, 22 per cent
226 F P	25	♂	20.7	Chronic prostatitis and vesiculitis	Trace of albumin, occasional cast
227 M R	63	♂	21.5 12.0	Chronic interstitial nephritis	Occasional cast
228 M S	45	♂	20.5 14.0	Chronic interstitial nephritis	Trace of albumin, many casts
229 A D	31	♀	20.5	Duodenal adhesions	

The urea estimations are made by a modified Marshall-Van Slyke method, essentially as described by Myers and Fine⁸. The enzyme used is that derived from the jack bean, the Nessler's solution, made according to the formula of Benedict and Bock, contains 100 gm of mercuric chlorid, 70 gm of potassium iodid and 200 gm of sodium hydroxid per liter of solution.

In our study of this series of analyses we have grouped the cases in six classes on the basis of urea concentration. Cases in which more than one determination was made are listed only in that group in which the highest determination falls. As it seemed desirable to show all evidence of renal impairment, we have also recorded the presence of albumin and casts in the urine, all blood pressures exceeding 150/90,

⁸ Myers, Fine and Lough. THE ARCHIVES INT. MED., 1916, 17, 570.

TABLE 7—CASES WITH UREA NITROGEN OF 25.1 TO 35 MG PLR 100 C C OF BLOOD

Case	Age	Sex	Urea N of Blood Mg per 100 C c	Diagnosis	Remarks
230 L	35	♂	29.0 14.5	Spastic paraplegia	Occasional cast, phthalein, 35 per cent
231 A M	48	♂	31.5	Hemiplegia	Occasional cast
232 A W	61	♂	34.2	Hemiplegia	
233 P L	24	♂	34.2	Bronchitis	Occasional cast
234 I P	28	♀	26.0	Chronic constipation	
235 A M	29	♂	28.0	Chronic endocarditis double mitral lesion	Occasional cast, phthalein, 31 per cent
236 M K	8	♂	26.0	Hemorrhagic purpura	
237 J G	56	♀	25.5 27.0 21.2	Diabetes mellitus	Trace of albumin
238 I S	40	♂	27.7	Diabetes mellitus	Blood sugar, 0.186 per cent
239 L H	56	♀	35.0	Diabetes mellitus Chronic interstitial nephritis	Blood sugar, 0.400 per cent
240 H G	21	♂	23.2 31.5 25.5	Chronic interstitial nephritis	Moderate amount of albumin occasional cast, creatinin 35, 38, 32 mg per 100 c c
241 S G	70	♂	26.0 28.0 26.0 14.8	Chronic interstitial nephritis and hyper- tension	Trace of albumin, phthalein, 11 per cent, 23 per cent, creatinin 43, 57, 64, 46 mg per 100 c c
242 M M	51	♀	31.7 35.0 22.2 28.0 16.5 20.0 28.5 33.5	Chronic interstitial nephritis and hyper- tension	Faint trace of albumin phthalein, 15 per cent, 9 per cent, 10 per cent, 8 per cent, 8 per cent, creatinin 55, 55, 44, 33, 30, 26 mg per 100 c c
243 P N	50	♂	27.0 19.5 11.1	Bronchial asthma, chronic parenchymatous nephritis	Moderate amount of albumin many casts, creatinin, 33, 46, 28 mg per 100 c c
244 W M	80	♂	28.0 24.8	Senility	Trace of albumin, moderate number of casts creatinin, 30, 38 mg per 100 c c

TABLE 8—CLASSIFICATION OF 206 CASES ON THE BASIS OF THE CONCENTRATION OF UREA NITROGEN OF THE BLOOD

	Urea N of Blood, Mg per 100 C c	Number of Cases	Percentage of Total Number
Group I	Less than 12.0	31	12.7
Group II	12.0-15.0	99	40.6
Group III	15.1-18.0	60	24.6
Group IV	18.1-20.0	16	6.5
Group V	20.1-25.0	23	9.4
Group VI	25.1-35.0	15	6.1

all phenolsulphonephthalein outputs of less than 40 per cent, all blood sugars of more than 0.16 per cent and blood creatinins of more than 3.5 mg per 100 c c

These six groups are given in detail in Tables 2 to 7, and are summarized in Tables 8 and 9. From Table 8 it can be readily seen

TABLE 9—PARALLELISM OF HIGH CONCENTRATION OF UREA NITROGEN IN THE BLOOD AND OTHER SYMPTOMS OF KIDNEY LESION

	Urea N of Blood, Mg per 100 C c	Number of Cases	Other Symptoms of Kidney Lesions	Percentage
Group I	Less than 12.0	31	11	35
Group II	12.0-15.0	99	38	38
Group III	15.1-18.0	60	26	43
Group IV	18.1-20.0	16	9	56
Group V	20.1-25.0	23	17	74
Group VI	25.1-35.0	15	12	80

that 84 per cent of the 244 cases examined have a urea nitrogen concentration of not more than 20 mg per 100 c c of blood. Table 9 shows that those groups in which the urea nitrogen of the blood is more than 20 mg per 100 c c contain a greater percentage of cases in which other factors give evidence of kidney lesion than do those groups in which the concentration of urea nitrogen is less than 20 mg per 100 c c. Furthermore, the detailed data of Tables 2 to 7 show that in those cases with a urea concentration of less than 20 mg, the other evidence of kidney lesion is generally so slight as to suggest no great loss of functional activity, but in those cases in which the urea concentration is more than 20 mg, the number and character of the other indications of kidney lesion are such as to suggest a more serious impairment of renal function.

On this basis, therefore, it seems reasonable to regard 20 mg per 100 c c as the upper normal limit of urea nitrogen in the blood of hospital patients, and, consequently, to regard all values above 20 mg as probably pathologic. This conclusion is not very different from that of Folin,⁹ who says that among strictly normal persons 14 to 15 mg is the maximum concentration of urea nitrogen, but that in hospital patients the values are quite as often between 15 and 20 as below 15.

The observations of Squier and Myers¹⁰ regarding the prognostic significance of the blood urea in sixty cases of prostatic obstruction are of interest in this connection. They conclude

Cases showing urea nitrogen figures under 20 mg per 100 c c of blood may be regarded as good operative risks, so far as the kidneys are concerned. When the urea nitrogen figures are found between 20 and 30 mg, and especially between 25 and 30, the patient should be operated on with considerable caution, and best after a period of preliminary treatment directed to relieve the nitrogen retention. With urea nitrogen figures over 30, the operative prognosis is bad.

⁹ Folin O. Jour Am Med Assn, 1917, 69, 1209

¹⁰ Squier, I B, and Myers, V C. Jour Urol, 1918, 2, 1

Study of this series convinces us, moreover, that as a means of estimating renal excretory power the determination of the urea concentration of the blood is, in itself, quite as satisfactory and far more practical than the determination of McLean's index¹¹ The difficulty of securing accurately timed specimens of urine from hospital patients needs no emphasis, and inaccurate specimens render the determination of the "index" quite futile But if the blood urea alone is made the criterion of kidney function, the physician himself can take the specimen and thus eliminate a frequent source of error

Even were it possible to secure accurate specimens of urine, we would still believe that the determination of the blood urea alone is quite as valuable as the determination of the "index" McLean¹¹ emphasizes the fact that in nephritis the blood urea frequently lies within normal limits, but the "index" is far below normal Cases 221, 227 and 228 of this series are of this type Our records show, however, that the first specimen of blood from these patients always has a moderately high urea nitrogen concentration, and that a diminution of protein in the diet is always followed by a rather slow but very definite diminution of urea nitrogen in the blood Since this is not characteristic of normal individuals, we believe that successive blood analyses are quite as valuable in the diagnosis of these cases as is the McLean index

SUMMARY

1 Of 244 hospital patients (medical cases) whose blood had a urea nitrogen concentration of less than 35 mg per 100 c c, 206, or 84 per cent, had a concentration of not more than 20 mg per 100 c c

2 Of these 206 cases only eighty-three, or 40 per cent, showed other evidence of renal impairment, but of the remaining thirty-eight cases, twenty-nine, or 77 per cent, showed other renal symptoms

3 From these observations we conclude that 20 mg per 100 c c may be taken as the upper normal limit of urea nitrogen in the blood of hospital patients, and that for diagnostic purposes the estimation of the blood urea is a satisfactory index of the functioning power of the kidney

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11 McLean, F C Jour Am Med Assn, 1916, 66, 415

THE EFFECT OF CONTINUOUS INTRAVENOUS INJECTIONS OF ETHYLHYDROCUPREIN ON EXPERIMENTAL PNEUMOCOCCUS INFECTIONS OF RABBITS *

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The invention of the Woodyatt¹ pump for maintaining intravenous injections over protracted lengths of time has led to the suggestion of several lines of research which are being developed in the Sprague Institute. One of these is presented in this article.

The effectiveness of the *in vivo* action of a therapeutic agent which is used because of its bactericidal properties, in all probability depends on the same factors which operate in the *in vitro* action of a bactericide, the two chief of which are the time factor and the concentration factor. Either *in vitro* or *in vivo* a given bactericide in a stated length of time will act better on bacteria in a higher concentration than in a lower one, and, in a stated concentration, will act better in a long time than in a short time. (It is important to realize that the latter is not infinitely true, since bacteria which are only inhibited or not entirely killed off by a certain low concentration will in time overcome the inhibition and become acclimated to the bactericide and thereupon grow unrestricted and probably with stimulation.) It is impossible to carry out a complete comparison of the *in vitro* action with the *in vivo* action of a chemical, because, in the first place, the concentration within the body is limited by toxicity, and in the second place, the concentration is constantly varying, because of (1) chemical destruction of the chemical or neutralization by oxidation or reduction, (2) chemical combination or conjugation with body constituents, and (3) excretion. The time factor, obviously, varies because of the same reasons.

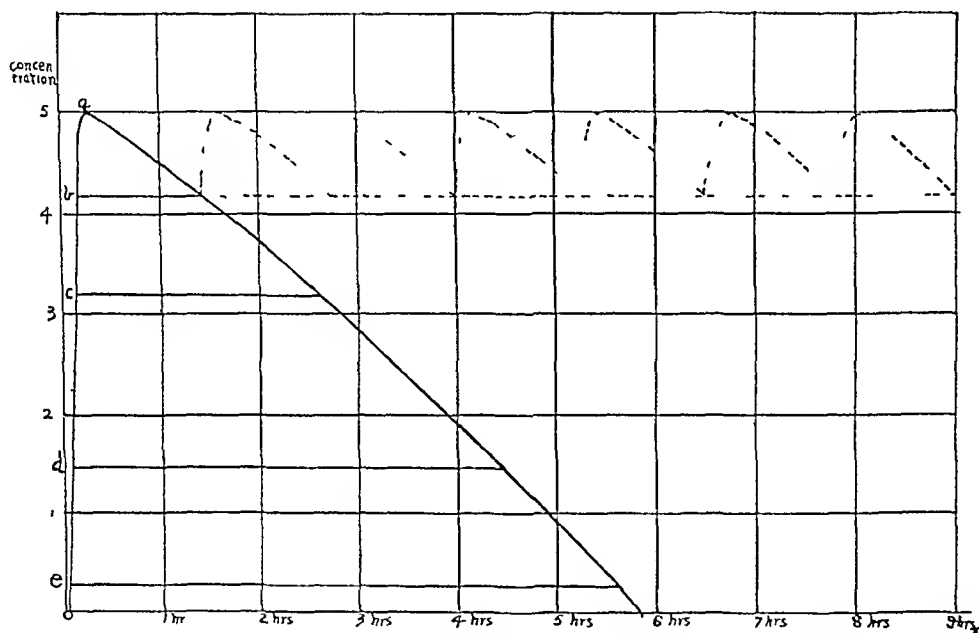
In our usual methods of administering a drug the curve representing the concentration of the substance in the blood at different intervals will be in the shape of a wave. The steepness of the ascent and descent of the wave will depend on the ratio of the rate of absorption and the size of the dose to the above three factors. The length of time which the drug is effective will depend on the shape of the curve and the concentration at which the drug can be effective.

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¹ From the Otho S. A. Sprague Memorial Institute and the Pathological Laboratory of the University of Chicago

¹ Woodyatt Jour Biol Chem, 1917, **39**, 355

Let the accompanying diagram represent the curve of concentrations which follow the intravenous injection of the largest possible dose of a drug which will not cause toxic symptoms. At once the concentration in the blood rises from zero to the point *a*. Let it be supposed that the three factors mentioned operate so that the concentration decreases at the rate represented by the descending portion of the curve. If the concentration at which the drug is active is at *a*, it is effective only a very short time, but if it is active at *b* it will be effective much longer, and so on, the time of effective action depending on the height of the wave, the rate of its decline, and the concentration of activity. An ideal drug can be pictured in this way showing that such a drug could obtain a high concentration (because of its non-toxicity), would be slow in decreasing this concentration, and would



be highly active at a low concentration. According to the curve, if the drug was active at the concentration *b*, there are two ways in which the time of action could be lengthened: one, by repeating the original dose, or fractions thereof, whenever the concentration fell to *b*. Schematically the concentration in the blood would then be represented by a series of small waves. The second way to maintain an effective concentration would be to introduce the drug *continuously* at a rate which would strike an equilibrium with the rate of operation of the factors which decrease the concentration. In this way the concentration would be schematically represented by a straight line. Such a process as this is now possible since the invention by Woodyatt¹ of a machine which is capable of delivering into the blood stream an accurate amount of fluid at a constant rate.

Let us compare these two suggested methods, first, with the more usual method of medication, and then with each other. While the maintenance of an effective concentration would enhance the action of a drug on bacteria, there would be an increased toxic action on the body tissues. This would, of course, be more marked the nearer the effective concentration approached the toxic concentration. The result would be either a fatal intoxication or a paralysis of the auxiliary forces which operate in the recovery from infections. In the latter case, unless the drug produces a *sterilisans magna*, the unkilld bacteria would be able to grow unrestricted in an almost inert organism. However, if the procedure should kill off all the bacteria, its use would be justified in spite of some toxic action. This is just exactly what does occur in some of our most important forms of medication, for example, in the treatment of syphilis, in which it is the usual procedure to obtain mercurialism and iodism in order to completely kill off the spirochetes. When the concentration is allowed to drop below effectiveness it is possible that in the intervals the bacteria will acquire a "drug resistance" which renders further treatment less effective. On the other hand, in giving frequently repeated doses to maintain an effective concentration, the toxic effect is apt to be more than in the maintenance of a constant concentration which is just effective, because, as represented schematically in the diagram, the concentration occurs in the form of small waves, the crests of which are above the effective concentration but which approach nearer the toxic concentration. In the continuous method a concentration that is above the effective one can be avoided.

It is purposed to follow up this line of research which is opened by the invention of the Woodyatt pump. The plan will be to study the curve of effective concentration in the blood stream, when various drugs are injected intravenously at a continuous and constant rate, on the various physiologic processes, and to put the method to actual test in treating disease conditions.

For various reasons the first drug the study of which has been undertaken in this manner is ethylhydrocuprein (optochin).

After the announcement by Moigenroth and Levy² of the discovery and properties of ethylhydrocuprein it was believed that this substance would play an important part in the therapy of pneumococcus infections in man. Quite contrary to these expectations, however, many reports subsequently appeared on the results obtained in its use in these infections, the general trend of which was that in pneumonia the effect of the drug was doubtful, not at all comparable to its *in vitro* action and to the striking cures obtained by Moigenroth in mice.

² Morganroth and Levy. Berl klin Wchnschr. 1911, 48, 1560 and 1679.

infected with the pneumococcus In the treatment of exposed pneumococcus infections, as corneal ulcers, where local applications can be made, the drug is of considerable value As to its value in other local infections, as pleuritis, peritonitis, arthritis, and meningitis caused by the pneumococcus, where direct applications of solutions of ethylhydrocuprein can be made, there seems to be no information

The studies of Moore³ present data which give the best information why ethylhydrocuprein is inactive in treating pneumonia He demonstrated that the drug is slow in action, has small powers of penetration, quickly disappears from the circulation, and has a toxic dose very close to its active dose For these very reasons, as pointed out in the foregoing, a possible advantage may be found in the continuous injection of the drug Moore himself anticipated this idea and adopted frequently repeated dosages in his treatments in human infections, but because of the theoretical advantages of the continuous injections over frequently repeated dosage we have not deviated from our purpose, in spite of his negative results

TECHNIC AND METHODS

Rabbits were chosen as the experimental animal because they are most suitable for the method In the first place, the easily accessible ear veins make repeated protracted injections possible and easy Again, the septicemia produced in rabbits by the pneumococcus makes an ideal condition for the *in vivo* testing of a bactericide Further, the experimental work that has been done on rabbits with ethylhydrocuprein, in which single dosages were given, has been with negative results⁴ If any beneficial results are obtained they may be justly attributed to the method used

The descriptions of the Woodyatt pump and its operation have been sufficiently made and a repetition will be omitted here

The first procedure was to find out the toxicity of ethylhydrocuprein when given intravenously for protracted periods at constant rates Amounts of the drug were weighed out and dissolved in an amount of 0.9 per cent sodium chlorid solution, so that when injected at the rate of from 18 to 30 c c per hour a certain number of milligrams per kilogram of body weight was delivered The water used for making the salt solution was redistilled from glass and the sodium chlorid was Merck's fused product The solution was filtered twice through hard filter paper and sterilized The syringe of the injecting machine, the buret, rubber tubing and needle were sterilized before

³ Moore and Chesney THE ARCHIVES INT MED, 1917, **19**, 611

⁴ Scott Jour Path and Bacteriol, 1914-1915, **19**, 130 Boecker Ztschr f Immunitätsforsch (Orig), 1915, **24**, 148

using. As it passed into the vein the fluid was warmed in a bath of warm water. In determining the toxicity, periods of six hours of injection were used and 2, 5, 10, and 15 mg per kilogram of body weight per hour were given. No symptoms of toxicity were obtained until 15 mg per kilogram per hour were given. The effect of this amount was inconstant. This amount could be given at times safely for ten hours. At other times death occurred during the first one or two hours of injection. No factor was found which was responsible for this variance. On the other hand, 10 mg per kilogram per hour could be given indefinitely without apparent toxic symptoms (ten-hour periods on three successive days), although in one instance sudden death occurred during the first hour of a second period of six hours each.

The effect on the bactericidal action of the serum for these rates was studied. Before the injection was started a sample of blood was taken from the heart. After three hours of injection another sample was taken, and another at the end of the injection. The serum from each sample was put in the ice box and next morning they were heated to 56 C for one-half hour. To equal amounts of each sample 0.5 c.c. of a 1:1,000,000 dilution of a twenty-four-hour broth culture of pneumococcus was added. At various intervals 0.1 c.c. was removed and plated with 10 c.c. of blood again. At the end of twenty-four hours the colonies on these plates were counted.

There was no effect on the bactericidal action of rabbit serum when ethylhydrocuprein was injected at a rate under 10 mg per kilogram-hour (Table 1). At this rate, however, there was a slight bactericidal effect, most pronounced at the end of injection. When given at 15 mg per kilogram-hour there was a rather marked bactericidal effect, most evident, also, at the end of injection (Table 2). This is the first time that it has been shown that ethylhydrocuprein can reach a bactericidal concentration in rabbit's serum, as other workers⁵ did not produce it when using single and repeated doses. It has been shown that the failure to obtain such a result with the drug is due to its rapid destruction in the liver (Scott⁴). We surmise that in the continuous injections the power of the liver to destroy or combine ethylhydrocuprein is either fatigued or that the rate of injection exceeds the rate at which the liver can act.

The next procedure was to find the influence of the continuous injection on infections produced in rabbits with the pneumococcus. A twenty-four-hour culture in serum broth of Type 1 was used as the infecting organism. Various intervals of time occurred between experi-

⁵ Wright. On Pharmacotherapy and Preventive Inoculation Applied to Pneumonia, 1915.

ments and the virulence of the organism varied, but each time the minimum lethal dose⁶ (M L D) was determined and the proper controls were made either with the same culture at the time of the ethylhydriocuprein experiment or the day before or after. The infecting dose was given intravenously and was immediately followed by treatment. At the end of each treatment a smear and culture were made from an ear vein, and on death a necropsy was held and cultures made of the heart's blood. The details⁷ are given in Table 3.

TABLE 1—EFFECT ON BACTERICIDAL ACTION OF RABBIT SERUM OF GIVING ETHYL-HYDROCUPREIN INTRAVENOUSLY AT THE RATE OF 10 MG PER KILOGRAM HOUR

	After 15 Minutes	After 35 Minutes	After 2 Hours	After 4 Hours	After 7 Hours	After 24 Hours
Normal serum	34		46	418		
Three hours of injection	44	18	28	31	24	
Seven hours of injection	97	25	19	44	98	

TABLE 2—EFFECT ON BACTERICIDAL ACTION OF RABBIT SERUM OF GIVING ETHYL-HYDROCUPREIN INTRAVENOUSLY AT THE RATE OF 15 MG PER KILOGRAM HOUR

	Immediately	After 30 Minutes	After 1 Hour	After 2 Hours	After 4 Hours	After 6 Hours	After 24 Hours
Normal serum	15	16	11	18	200	1 000	
Three hours of injection	14	16	18	10	18	46	
Seven hours of injection	19	17	6	6	3	0	0

The results of the experiments can be summarized shortly by saying that in no case was any beneficial effect on the infected animals observed, and in some cases the treated animals died sooner than the controls.

Two modifications of the routine method of treatment were made in an effort to eliminate certain factors which may have been responsible for the negative results. When 21 c c are given each hour intravenously, at the end of ten hours there has been injected in all 210 c c. If no urine, or only a small amount, is excreted in ten hours, the volume

6 A minimum lethal dose is one that will kill within twenty-four hours. If a rabbit overcomes an infection for from thirty-six to forty-eight hours it is not likely to die at all, and in order to be sure of a fatal dose the twenty-four-hour period was selected.

7 At the end of each injection blood cultures were made from an ear vein, and at death smears and cultures were made from the heart's blood, in every case these were positive, and in the last experiment a count of the bacteria showed four times as many in the blood as with the control.

of blood had practically been doubled, which, besides decreasing the concentration of ethylhydrocuprein also decreases the concentration of antibodies. To obviate this the drug was given in a 2 per cent sodium chlorid solution, which is markedly diuretic. Nevertheless, no improvement in the results was obtained.

Another modification was to give a large initial dose at once and to follow this immediately with periods of continuous injections of 15 mg per kilogram-hour, of three hours each. The results differed in no way from the others.

TABLE 3—RESULTS OF TREATING RABBITS INFECTED WITH PNEUMOCOCCUS WITH ETHYLHYDROCUPREIN INJECTED INTRAVENOUSLY *

Weight of Rabbit, Gm	Amount of Optochin per Kilo Hour, Gm	Amount of NaCl Solution per Hour, Cc	Hours of Injection	Dose of Pneumococcus	Results of Treatment
1,670	0.0082	18	7	1 24 hour slant (5 M L D)	Dead within 24 hours
1,625	0.0074	18	7	1 24 hour slant (5 M L D)	Dead within 24 hours
2,157	0.010	18	First period, 6 hours, second period (after 3¼ hours' interval) 4 hours	2 c.c. of broth culture (5 M L D)	Dead within 24 hours
1,830	0.011	21	First period, 6 hours, next morning, 6 hours	1 c.c. of broth culture (2 M L D)	Died suddenly at the close of second injection
1,680	0.01	21	6	0.5 c.c. of broth culture (5 M L D)	Died within 24 hours
1,700	0.01	21	6 hours after 3 hour interval, 1 hour	0.1 c.c. of broth culture (10 M L D)	Died during injection
1,747	0.01	21	8	0.001 c.c. of broth culture (1 M L D)	Died within 24 hours

* This protocol lists only typical experiments and does not include all experiments done.

While these results do not bear out the theory at the basis of continuous intravenous injections, it is probably because of the nature of the drug and not because of the method. These results lead to the same conclusions as those of Moore, that the drug is useless in the routine treatment of pneumonia.

It is possible that a study of the action of ethylhydrocuprein given continuously in this way on the action of antibodies may explain in some way the paradoxical fact that the pneumococcus septicemia progresses in spite of a demonstrable bactericidal action of the serum.

SUMMARY

1 Ethylhydrocuprein can be given to rabbits intravenously and continuously over protracted lengths of time at the rate of 10 mg per kilogram per hour, without apparent toxic effects.

2 When injected intravenously into rabbits at the rate of 10 mg per kilogram per hour for seven hours, ethylhydrocuprein produces

a slight bactericidal action of the serum. A much higher bactericidal action is produced when it is injected at the rate of 15 mg per kilogram per hour for seven hours.

3 The effect of a fatal dose of pneumococcus on rabbits is not affected by the continuous intravenous injection of ethylhydrocuprein, in spite of the fact that the animal's blood may be distinctly bactericidal *in vitro*.

4 The continuous intravenous injection of a soluble bactericidal therapeutic drug has theoretical advantages over the usual single or intermittent dosage. The failure of the method with ethylhydrocuprein is probably due to the nature of the drug and not to the method.

AN EXPERIMENTAL STUDY OF SERUM THERAPY IN TRICHINOSIS

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DETROIT

Salzer¹ has published a study of trichinosis in which he claims to have secured beneficial results in man and in experiment animals by the use of serum from patients recovered from the disease. In this connection he also claims that injections of serum are prophylactic against trichinosis, that animals fed with infected meat within twenty-four hours after the administration of the serum might develop a mild form of trichinosis, but if fed at a later period would prove to be immune, and that if immune serum was mixed with infected meat and then fed to animals, the animals did not develop trichinosis, though the ingestion of the same meat without serum was invariably followed by the appearance of the disease. In two patients in the active stages of trichinosis the administration of the serum showed remarkable curative power, there was a decided drop in temperature within six hours and the normal temperature had entirely subsided within twenty-four hours.

Schwartz² has categorically taken up Salzer's claims and rejected them, largely on the basis of animal experimentation, in the following language:

1 Serum from animals convalescent from trichinosis when injected into other animals did not produce immunity to trichinosis in the latter. 2 Trichinous meat mixed with serum from animals during the active or convalescent stage of the disease proved to be still capable of producing the disease. 3 Animals once infected and harboring trichinae in their muscles were not immune to further infection when fed trichinous meat. 4 Serum from a trichinous animal had no observable ill effects on the larvae freed from their cysts by artificial digestion. 5 None of the results of the experiments appear to be in harmony with the assertions made by Salzer concerning the value of serum from convalescent animals as a prophylactic or curative agent in trichinosis.

We have carried out a number of experiments in testing the prophylactic and curative value of serum from animals recovered from trichinosis, and have come to the following conclusions. So far as our experiments are comparable to those performed by Schwartz, our findings are in agreement with his and tend to disprove Salzer's specific contentions along these lines, but we believe that in spite of

* Submitted for publication June 19, 1918

* Research Laboratory, Parke, Davis and Company

1 Salzer, B F Jour Am Med Assn, 1916, **67**, 579

2 Schwartz, Benjamin Jour Am Med Assn, 1917, **69**, 884

some erroneous contentions, Salzer may be right in part of his assertions and the treatment he suggests worthy of more approval than Schwartz is inclined to accord to it

The reason we both agree and disagree with Salzer and with Schwartz is that there are two phases of trichinosis which are not differentiated by either of these writers, though each stands on good ground according to the phase he is considering. Trichinosis is a disease due to the presence in the body of the worm called *Trichinella spiralis* (*Trichina spiralis*). One phase of the disease is a mechanical phase, due to the presence and actions of the worm in the digestive tract, the blood stream, and the musculature. The other phase of the disease is chemical in nature and is due to the presence in the blood of the more or less toxic excretions and secretions of the worm. The first phase of the disease sets up an inflammatory defense reaction which terminates in the walling-in and sealing of the worm cyst in the muscles. The second phase of the disease sets up the customary antibody defense reaction of the blood, which defense reaction becomes manifest in an eosinophilia that may go as high as 86 per cent and which presumably terminates when the sealing of the worm cyst prevents the excretion and secretion products from reaching the blood stream and when those already present are neutralized or otherwise disposed of and rendered innocuous by the blood.

As regards the first phase, in our opinion, serum has little or no power to prevent the development of the larval worms to adults in the intestines, to prevent the embryo worms from invading the blood stream and tissues, and to prevent these embryo worms from encysting and developing to infective larvae. The experiments performed by Schwartz and ourselves bear out this contention, and so far as Salzer claims the contrary, we believe he is in error.

The claim is occasionally made that worm infestations produce immunity to subsequent infestations with the same worm. For most worms there is a great deal of evidence against the belief and but a small amount in favor of it. It has recently been claimed by Fujinami for schistosomiasis.

As regards the second phase, there seems to be no evident reason why serum from an animal that has recovered from trichinosis should not be of value in protecting another animal from the toxic effects of the secretions and excretions of the worms. These materials, be they specific secretions or waste products of the worm's metabolism, must act like any other foreign protein in the blood in the production of antibodies, and recovery from the disease represents not only the survival of the mechanical damage due to the worm, but an adequate production of antibodies to offset the deleterious effect of these toxic proteins on the body economy. In this connection it might also be

noted that while worm infestations in general are typically afebrile conditions, trichinosis in man is typically febrile, and that the production of the high temperatures has been attributed by some workers to the invasion of the tissues and blood stream by bacteria accompanying the worms. There is exactly the same reason to suppose that the serum of an animal which has recovered from trichinosis would be of value in supplying readymade antibodies to combat toxic worm products, and perhaps accompanying bacterial products, in a case of trichinosis, as there is for believing that serums from immune animals are of value in diphtheria or tetanus. In this respect we are in agreement with Salzer as to the probable value of such a serum, and believe that Schwartz has not attached enough importance to this phase of the subject.

EXPERIMENTS

In undertaking our experiments we first infected a dog in order to obtain a supply of serum. The trichinous pork for feeding to start the experiments was obtained through the kindness of Dr B. H. Ransom, chief of the Zoological Division of the United States Bureau of Animal Industry, who has made some notable contributions along the line of control of trichinosis through the federal meat inspection service. The infected meat was fed in small lots to two dogs, as follows:

Dog 127—A mongrel hound weighing 115 kg, was given 2 gm of the meat. Daily examinations of the feces for the next twenty-six days did not show the passage of any trichinae. On the twenty-sixth day the dog was bled from the jugular and then killed with chloroform. Examination of the diaphragm did not disclose any trichinae. The animal may have had a light infection, which was not detected, or it may have been immune to trichinosis, as dogs are commonly resistant to the development of trichinae. Such resistance to infection with species of worms other than those customarily found in a given host species seems to be more a matter of nice adaption to host morphology, temperatures, chemical reaction of the gastro-intestinal secretions, and such inherent physical and chemical conditions, than a matter directly related to any of the blood reactions commonly concerned in immunity.

Dog 129—A mongrel weighing 15 kg was given 3 gm of trichinous meat, twenty-five days later it was fed 2 gm more, ten days later it was fed 2 gm more, eleven days later it was fed 4 gm more, four days later it was fed 4 gm more, five days later it was fed 5 gm more, six days later it was fed 5 gm more, eight days later it was fed 64 gm more, a total of 89 gm of trichinous meat. The dog remained active throughout the experiment and did not appear diseased or uncomfortable except for a keratitis beginning the second day after the first feeding and disappearing eighteen days later. The dog was bled from the jugular under chlorotone anesthesia 111 days after the first feeding and forty-two days after the last feeding, and the serum separated and preserved with 0.4 per cent trikiesol. The diaphragm was found to be fairly well infested with trichinae.

The animals used for the tests of the serum were white mice. They are easy to infect, but they show little clinical evidence of the disease, so that our tests of efficacy are primarily a consideration of

the longevity of infected rats treated with serum in comparison with check animals similarly infected but not treated, all animals being kept, so far as possible, under identical conditions of temperature, food, water, etc. The rats were run in series of two to six, one or more serving as checks, and the others receiving various treatments.

We tried guinea-pigs first, feeding them from the same trichinous pork with which the dogs had been fed, but experiments with twelve of them showed that the meat was but slightly infective at this time or the guinea-pigs were resistant, so the diaphragm of Dog 129 was used as the initial infective material and the guinea-pigs dropped in favor of rats. The supply of trichinous meat was kept up by feeding dead experiment rats to new experiment rats. The experiments follow.

Series 1—To Determine Whether Serum Affects Trichina Larvae

Rat 1 was fed 10 gm of the diaphragm of Dog 129 and six days later was fed 13 gm more. Thirty-four days later the rat received a subcutaneous injection of 1 cc of the serum from Dog 129. The rat was killed nine days later and the muscles found infested. It was used to infest other rats.

Rat 2 was fed the same amounts at the same time as Rat 1. It was injected the same day, but received 2 cc of serum. It died forty-four days after the injection, and the muscles were found infested and infective for other rats.

This experiment only indicates that serum exerts no evident bad effect on trichinae when used at the interval and in the amount given, the trichinae being alive and infective for susceptible animals.

Series 2—To Determine the Effect of Simultaneous Injection and Feeding

Rat 1 was fed 1 gm of meat from Rat 1 of Series I, and was injected at the same time with 1 cc of serum. The rat escaped while a temperature was being taken and was soaked with cold water before it was captured. It was found dead the next day. Postmortem examination showed pneumonia. This animal cannot be considered in determining the results of the experiments.

Rat 2 was fed 1 gm of meat from Rat 1 of Series 1, and was injected at about the same time with 2 cc of serum. The following day it was fed 1 gm more of the meat. Two days after this second feeding the rat was almost dead, so it was killed. The intestine was hemorrhagic and scrapings showed numerous trichinae.

Rat 3, the check, was fed the same amounts and at the same time as Rat 2, but was given no serum. This rat died either the afternoon of the day it was fed the second time or the following day. The intestine was hemorrhagic and showed numerous trichinae, especially in the duodenum.

In this experiment the treated animal outlived the check a short time, one or two days.

Series 3—To Test the Prophylactic Value of Serum Simultaneously Injected or on Food

Rat 1 was fed 2 gm of trichinous meat and was injected at the same time with 1.5 cc of serum. Eight days later it was fed 1 gm more. Forty days after the second feeding it was fed 1 gm more. Six days after this last feeding the rat was killed. The muscles were heavily infested.

Rat 2 was fed the same amounts and at the same time as Rat 1, but the first feed of trichinous meat was mixed with 5 cc of serum before feeding. In addition to the feedings at the same time as Rat 1, this rat was fed 1 gm of meat the day Rat 1 was killed. Four days later it was fed 1 gm more, six days after this feeding it was fed 1 gm more. Five days after the last

feeding it was found dead. The intestine was hemorrhagic and contained trichinae. Trichinae were abundant in the muscles.

Rat 3, a check, was fed the first two times that the others were fed, getting the same amount of trichinous meat. Two days after the second feeding the rat was found dead. No trichinae were found in the diaphragm or intestines.

In this experiment the rats receiving the serum outlived the check rat decidedly, but it was impossible to associate definitely the death of the check animal with the feeding of trichina. Experiments show, however, that neither the injection nor the feeding of serum prevented infection with trichinae.

*Series 4—To Test the Prophylactic Value of Serum Simultaneously
Injected or on Food*

Rat 1 was fed 1 gm of meat mixed with 1 cc of serum. Additional feedings of 1 gm each were made on the third, tenth, fourteenth and twentieth days after the first feeding, but no serum was given with these feedings. The day after the last feeding the rat was found dead. The intestines were hemorrhagic and the lungs pneumonic. Trichinae were found in the intestines and musculature.

Rat 2 was fed the same amounts and at the same time as Rat 1, but the first gram of meat was mixed with 2 cc of serum. Following the death of the first rat, No 2 was fed additional meat as follows: 24 days after the first feeding, 0.5 gm; 28 days, 1 gm; 38 days, 1 gm; 45 days, 2 gm; 52 days, 1 gm; 57 days, 1 gm; 63 days, 1 gm; 68 days, 0.5 gm. The rat died the day after the last feeding. The lung was pneumonic and presented tubercles, the nature of which was not determined. There were trichinae in the intestine and the musculature showed a very heavy infestation. Trichinae were present in the scalp muscles, the eye muscles and in some coats of the eye.

Rat 3 was fed the same amounts and at the same time as Rat 1, but received an injection of 1 cc of serum when the first gram of meat was fed. This rat died five days after Rat 1. The stomach and small intestine were hemorrhagic and the lungs pneumonic. There were trichinae in the intestine and musculature.

Rat 4 was fed the same amounts and at the same time as Rat 2, but received an injection of 2 cc of serum at the time the first gram of meat was fed. This rat also received an additional 0.5 gm of meat seven days after the last feeding of Rat 2. Ten days after this feeding the rat was found dead. This rat showed a pronounced edema of the eyelids and the left eye became purulent and blind. Trichinae were found in the intestine and the muscles were heavily infested.

Rat 5, a check, was fed the same amounts and at the same time as Rat 1, but received no serum. In addition it was fed 0.5 gm of meat four days after the last feeding of Rat 1, and 1 gm eight days after the last feeding of Rat 1. Two days later the rat began to develop nervous symptoms. It would fall to the right side and could hardly assume or maintain an erect position. Four days later the condition was more marked and the rat would roll over and over to the right unless restrained by some limiting object on that side. Eight days after its last feeding the rat was found dead. The intestine was hemorrhagic and the lungs pneumonic. Trichinae were found in the intestine and in the diaphragm.

Rat 6, a check, was fed the same amounts and at the same time as Rat 5. In addition it was fed 1 gm of meat ten days after the last feeding of Rat 5 and 2 gm seventeen days after the last feeding of Rat 5. Eight days after its last feeding the rat was found dead. There was a severe hemorrhagic condition in the jejunum, less severe in the duodenum, and the lungs were pneumonic. Trichinae were found in the intestine and diaphragm.

It will be seen from the foregoing that the serum, injected or fed with the trichinous meat had no evident prophylactic value.

As regards the curative value of the serum, as judged by comparative longevity of the treated animals and the checks, we find the following

Two of the treated animals, those receiving the largest amounts of serum by injection or feeding, outlived both the checks, and both the checks outlived the other two treated animals, those receiving the smallest amount of serum by injection or feeding. As the feedings were kept up, the survivors in all cases received larger amounts of meat than the animals outlived by them. The animals receiving the larger amount of serum outlived the checks by totals of 120 days, while the checks outlived the animals receiving the smaller amount of serum by totals of eighty-four days. This leaves a slight presumption in favor of the idea that there is some value in the treatment. The severity of infestation in Rats 2 and 4 may be fairly associated with their additional feedings.

*Series 5—To Test the Prophylactic Value of Simultaneous and
3 and 4 Cc Injections of Serum*

Rat 1 was fed 2 gm of meat and at the same time was given a subcutaneous injection of 3 cc of serum. Seven days later it was fed 2 gm more of meat, seventeen days later, 2 gm more, twenty-four days later, 1 gm more, and twenty-nine days after the first feeding was fed 1 gm more. Two days later the rat was found dead. The lungs showed hepatized areas, the liver was light colored and apparently degenerated. Trichinae were found in the intestine, and the diaphragm was rather lightly infested.

Rat 2 was given two feedings at the same time that Rat 1 received its first two, and got the same amounts, but was given an injection of 4 cc of serum at the time of the first feeding. Seventeen days after the first feeding it was found dead. The lungs showed areas of hepatization and there was some blood in the intestine. Trichinae were plentiful in the intestine, but the diaphragm was very lightly infested.

Rat 3, a check, was fed four times at the time Rat 1 received its first four feedings, and received the same amounts as Rat 1. Five days after the last feeding this rat was found dead. The lungs were pneumonic and the jejunum hemorrhagic. There were trichinae in the intestine and the diaphragm was very heavily infested.

While the injections of large amounts of serum, 3 or 4 cc, did not prevent infestation with trichinae in Rats 1 and 2, it is nevertheless interesting to note that these rats, which had been fed five times and two times, had very light infestation with trichinae, while the check rat, which was fed four times, had a very heavy infestation.

As regards longevity, a treated rat outlived the check nine days and the check outlived the other treated rat five days, a margin in favor of the treated animals.

*Series 6—To Test the Prophylactic Value of Injections
Previous to Feeding*

Rat 1 was injected with 1 cc of serum and fed 1 gm of heavily infested meat the next day. One week after each of these proceedings, the injection and the feeding were repeated. Five days after the second injection of serum it was repeated, followed by the feeding of a gram of the meat the next day, making a total of three injections of 1 cc of serum followed each time by feeding 1 gm of meat the next day. Four days after the last feeding the rat was found dead. The lungs were pneumonic. A moderate number of trichinae were found in the intestine, but none in the diaphragm at that date.

Rat 2 received the same treatment, as regards serum and trichinous meat, that Rat 1 received. This animal lived and enjoyed good health for fifty-eight days and was killed at that time to permit of postmortem observations and to close up the experiment. The anterior portion of the right lung presented tubercles and was adherent to the chest wall at this point. There were no

trichinae found in the intestine and only a very moderate number in the diaphragm

Rat 3, a check, was fed the same amount of trichinous meat at the same time as the other rats, but was given no serum. This rat died five days after the last feeding. The intestine was hemorrhagic and heavily infested with trichinae. No trichinae were found in the diaphragm at this time.

As regards longevity, the check outlived one treated animal by one day, but the other treated animal outlived the check by thirty-nine days and was killed when it had evidently outlived any danger from its trichina feeding and apparently would have lived much longer.

As regards development of trichina, the check rat had a much larger number in the intestine than the treated Rat 1, these two rats did not show somatic trichinosis, but died too soon to permit of conclusions in regard to this. Rat 3 lived long enough to lose its intestinal trichinosis and had acquired a mild somatic infestation.

SUMMARY OF EXPERIMENTAL DATA

A summary of the foregoing data on longevity shows. Of fifteen rats, those given the serum treatment outlived the checks in nine cases, whereas the checks outlived those given the serum in six cases. In two cases the treated animals were killed instead of being allowed to die. The figures for each series are as follows:

Series 2. Treated animal outlived the check by one or two days.

Series 3. Treated animals lived an average of 62.5 days, the check, 11 days. Treated animals lived on an average 51.5 days longer than the check.

Series 4. Treated animals lived an average of 51.25 days, checks, 45.5 days. Treated animals lived on an average 5.75 days longer than the checks.

Series 5. Treated animals lived an average of 25 days, the check, 23 days. Treated animals lived on an average 2 days longer than the check.

Series 6. Treated animals lived on an average 37 (plus) days, the check, 18 days. Treated animals lived on an average 19 (plus) days longer than the check.

Note that treated animals outlived the checks in every series, the total number of days which treated animals survived the checks being 80 (plus).

From what we know of antibody production it appears, then, entirely likely that serum from an animal recovered from trichinosis would be of value in combating the toxic features of the disease. Our experiments seem to bear out this idea. The experiments are by no means proof of the value of the treatment, but they are evidence which accords with the theoretic possibilities and with Salzer's good clinical results in two of his cases, which results deserve to be considered apart from what appear to be undemonstrable claims in regard to serum inhibition of trichina development.

The clinical picture of trichinosis in rats is not a well defined affair as in man. Rats are the habitual and normal hosts of trichinae and probably have an inherent tolerance for these worms. Raebiger³ found no eosinophilis in the blood of trichinous rats and but few eosinophils around the encysted trichinae, though Opie⁴ found eosinophilia beginning at the end of the second week. Rats show little evidence of myalgia and the pyrexia present in man seems to be lacking. The day after rats are fed trichinae there is usually a marked fall of temperature, followed by a rise to normal the following day, or a slow rise for several days. Such data as we have on this point (temperatures were not taken on Sundays) shows that twenty-four hours after feeding trichinous meat without serum in any form, the temperature dropped 42 times, an average drop of 1.9 degrees, and rose 19 times, an average rise of 1.1 degrees. Where trichinous meat was fed and serum injected at the same time the temperature dropped 5 times, an average of 0.96 degree, and rose once, 1 degree. Where trichinous meat was fed after being mixed with serum the temperature dropped in both of two cases, 0.3 and 1.2 degrees. Where serum was injected without trichinous meat being fed the same day the temperature dropped 4 times, an average of 0.56 degree, and rose 4 times, an average of 0.7 degree. The greatest fall of temperature followed by recovery was in the case of Rat 1 of Series 4, on the third feeding the temperature dropped from 99.8 F the day of feeding to 95.5 the following day, a drop of 4.3 degrees, but rose to 99 the next day. The greatest rise in temperature was in the case of Rat 4 of Series 4, on the sixth feeding the temperature rose from 97.6 to 101, a rise of 3.4 degrees.

The usual fall in temperature seems to be associated with a marked enteritis. There is usually blood in the feces and rectum the day after feeding trichinous meat, a condition that may visibly persist for as many as four days after feeding. Associated with this is a diarrhea and more or less gas in the intestine. Pneumonic conditions were rather common in these rats, perhaps due to the passage of embryos through the pulmonary capillaries. The edema of the eyelids, which is comparatively common in trichinosis in man, was only detected once in our rats.

The fact that rats are extremely tolerant of trichinae and do not present a clinical picture comparable to that in man, and the fact that other experiment animals are open to the same objection (experimental feeding to a shoat failed to develop pyrexia, though 83 gm of trichinous meat were fed in thirty-three days) or are open to the objection

3 Raebiger, S. Ztschr f Infektionskr d Haustiere, 1911, 9, 120

4 Opie, E. L. Am Jour Med Sc, 1908, 127, 477

that they are difficult to infect, suggests that the value of immune serum in trichinosis can hardly be ascertained except by clinical test on human patients. The lack of febrile conditions in rats, or in the shoat just mentioned, suggests that in these animals there is an inherent immunity to the second phase of trichinosis, the phase associated with toxic products in the blood and with antibody production against the toxins. Rats and swine have presumably acquired this immunity through ages of infestation and apparently suffer primarily from the first phase of the disease, the mechanical phase, against which no immunity could readily be developed. Man, in a comparatively short and limited experience in feeding on raw trichinous pork, has developed no such immunity to the second phase of trichinosis.

In view of the fact that our present day treatment of trichinosis is mostly palliative and symptomatic, a serum treatment might be of considerable therapeutic value. Its commercial value would be slight. The number of cases of trichinosis in the United States yearly is not large, the serum from one horse which had been properly immunized by feedings of trichinae would probably more than supply treatment for all cases. Such production could only be profitably undertaken by a firm selling directly from a central plant, it could not be profitably undertaken by a firm with numerous branch houses to be restocked yearly.

SUMMARY AND CONCLUSIONS

Our experiments bear out the conclusions of Schwartz to the effect that serum from animals convalescent from trichinosis, when injected into other animals or fed to them mixed with trichinous meat, does not inhibit the customary development of trichinae.

On the other hand, theoretic considerations, the clinical observations of Salzer, and the longevity data from our experiments lead us to the conclusion that such a serum may be of decided value in combating the toxic features of trichinosis, a conclusion which is in general agreement with Salzer's belief in the value of such a serum.

METABOLISM IN A CASE OF HEMOCHROMATOSIS

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Meltzer,¹ in 1900, and Parker,² in 1903, suggested that the deposition of iron-containing pigment in the tissues in hemochromatosis was in part the result of faulty retention of iron. This view was given support in a more recent article edited by Garrod³ in which Mackenzie Wallis stated that no iron was found in the feces, urine, or bile of a case of hemochromatosis while a slight increase in the iron content of the blood was present. Mackenzie Wallis was unable to carry out metabolism studies in his case, but he emphasized the importance of such work. Howard and Stevens⁴ have recently reported the first accurate metabolism studies in this disease. Their publication gives an excellent discussion of what is known concerning its chemistry. In the report here presented additional metabolism studies on a case of hemochromatosis have been made.

METHODS

The patient was given the following diet

FOOD MIXTURE

Milk	625 cc
Cream (40%)	275 cc
Eggs	550 gm
Malted milk	60 gm
Water up to	2,500 cc

This diet did not exceed the carbohydrate tolerance of the patient as judged by the absence of sugar from the urine throughout the period of the metabolism experiment. Feedings were given at two hourly intervals from 7 a m to 7 p m. With each of the first morning feedings the patient was given a gelatin capsule containing from 0.187 to 0.210 gm of ferric ammonium citrate. The stools at the beginning and the end of the experiment were demarcated by adding 2 gm of charcoal to the first and last feedings. The patient was given the diet one day prior to beginning the collection of specimens. The metabolism experiment was of five days' duration. All the stools were collected in porcelain containers, mixed with 2 per cent hydrochloric acid in

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^{*} From the medical clinic of the Peter Bent Brigham Hospital

1 Meltzer, S J. The Pathogenesis of General Hemochromatosis (Diabete bronzé). *Med Rec*, New York, 1900, **57**, 43

2 Parker. Case of Bronze Diabetes. *Brit Med Jour*, 1903, **2**, 1052

3 Gaskell, J F, Sladden, A E, Mackenzie, Wallace R L, Vaile, P T, Garrod, A E. A Contribution to the Study of Bronze Diabetes. *Quart Jour Med*, 1913-1914, **7**, 129

4 Howard, C P, and Stevens, F A. The Iron Metabolism of Hemochromatosis. *THE ARCHIVES INT MED*, 1917, **20**, 896

95 per cent alcohol and dried to constant weight at 50 C. Aliquot portions of each day's food were mixed and kept under toluol on ice. The urine was preserved under toluol on ice.

Nitrogen was determined by the Kjeldahl method and ammonia by the aeration method of Folin⁵. Iron was determined by the method of Neumann⁶. The total sulphur was quantitated by Benedict's⁷ method. The food and feces were prepared for the sulphur determination in the way outlined by Baumann and Howard⁸. To determine phosphorus the food, feces or urine were first ashed by Neumann's method. The phosphorus was precipitated as ammonium phosphomolybdate and determined volumetrically. Calcium and magnesium were quantitated by McCrudden's method⁹. The food and feces were prepared, in the analysis for calcium and magnesium, by the procedure outlined by Baumann and Howard. Potassium and sodium were determined in the solution obtained by ashing according to Neumann's method. They were obtained as the chlorids and then the potassium as the chloroplatinate by the usual methods. In determining chlorin, sodium carbonate (Na_2CO_3) was added to the urine or food and the whole evaporated to dryness in a platinum dish on the water-bath. The residue was incinerated, avoiding red heat. The ash was extracted with cold nitric acid (HNO_3), the residue heated until white, the acid extract added and the whole evaporated to dryness. The residue was extracted with dilute nitric acid and the chlorin titrated according to Mohr's method¹⁰. Urea was determined by the method of Van Slyke and Cullen,¹¹ and total nonprotein nitrogen in the blood by that of Folin¹². Blood fats were estimated by Bloor's method¹³. The basal metabolism was determined by the method of indirect calorimetry. The usual mask covering the nose and mouth was used. The expired air was collected in a Tissot spirometer. Analyses for oxygen (O_2) and carbon dioxide (CO_2) were made with the Haldane gas analysis apparatus. The patient was kept at complete rest in bed without food or drink for eight hours prior to running the basal metabolism experiment.

5 Folin, O. Aeration Method for the Determination of Ammonia. A Laboratory Manual of Biological Chemistry. New York, 1916, p. 79.

6 Neumann, A. Einfache Veraschungsmethode (Sauregemisch-Veraschung) und vereinfachte Bestimmung von Eisen, Phosphorsaure, Salzsäure und anderen Aschbestandtheile unter Benutzung dieser Sauregemisch-Veraschung. Ztschr. f. physiol. Chem., 1902-1903, **37**, 115.

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8 Baumann, L., Howard, C. P. Metabolism of Scurvy in an Adult. THE ARCHIVES INT. MED., 1912, **9**, 665.

9 McCrudden, F. The Quantitative Separation of Calcium and Magnesium in the Presence of Phosphates and Small Amounts of Iron Devised Especially for the Analysis of Foods, Urine and Feces, Biol. Chem., 1910, **7**, 83. The Determination of Calcium in the Presence of Magnesium and Phosphates. The Determination of Calcium in Urine, Jour. Biol. Chem., 1911, **10**, 187.

10 Hawk, P. B. Practical Physiol. Chem., Philadelphia, 1916.

11 Van Slyke, D. D., and Cullen, G. E. A Permanent Preparation of Urease and Its Use in Determination of Urea, Jour. Biol. Chem., 1914, **19**, 211.

12 Folin, O., and Denis, W. Nitrogen Determinations by Direct Nesslerization. II. Nonprotein Nitrogen in Blood, Jour. Biol. Chem., 1916, **26**, 491.

13 Bloor, W. R. Nephelometric Method for the Determination of Fat in Blood, Jour. Biol. Chem., 1911, **17**, 377. A Method for the Determination of "Lecithin" in Small Amounts of Blood, Jour. Biol. Chem., 1915, **22**, 133. The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, Jour. Biol. Chem., 1916, **27**, 107.

SYNOPSIS OF THE CASE REPORT

History—W W S, Med No 6565, white man, aged 52, was admitted to the Peter Bent Brigham Hospital, May 7, 1917, and discharged improved June 3, 1917. Complaint, "weakness and sciatica." The family and marital history are unimportant. Habits. The patient did not use alcoholic drinks. He used tobacco in moderation, but took no drugs. Occupation. Police officer. He stopped work April 8, 1917, because of present illness.

Past Medical History—The patient was born in Scotland and had lived in America forty-five years. He had scarlet fever as a baby, influenza nineteen years and typhoid fever nine years prior to admission. He had had a broken arm and four broken ribs. A hydrocele was tapped in October, 1916. The past medical history was otherwise negative.

Weight. Patient weighed 215 pounds five years prior to admission. His present weight was 180, 25 pounds having been lost since January, 1917.

Present Illness—For several years the patient had had occasional attacks of sciatica-like pains in the right thigh. Since January, 1917, this symptom had grown worse and was constantly present on admission to the hospital. Since that time he had become progressively weaker physically. For the last few weeks there had been a sensation of numbness beginning in the lips and radiating down the left arm. Polydipsia, polyphagia or polyuria were not present.

Physical Examination—The patient was a well developed, fairly well nourished although somewhat gaunt looking man. The skin of the neck, face, forearms and legs was diffusely pigmented and dark brown in color. The skin of the remainder of the body was also pigmented but to a less degree. Liver dullness began at the fifth rib anteriorly. The edge of the liver was palpable 5 cm below the costal margin in the right mammary line. It was smooth and nontender. The spleen was palpable 2 cm below the left costal margin. The edge was sharp, firm and nontender. Examination of the heart gave no abnormal findings. Blood pressure was 115 mm systolic and 65 mm diastolic. There was some stiffness and pain in the right knee on motion. A roentgenogram of the joint showed hypertrophic bony changes. The remainder of the physical examination was negative.

Laboratory Findings—May 7. Blood examination. Hemoglobin was 75 per cent (Sahli). White cells were 5,600 per cmm. The differential count was 50 per cent polymorphonuclears, 45 per cent lymphocytes, 5 per cent large mononuclears. May 31. Hemoglobin was 88 per cent, red cells were 5,680,000 per cmm, and white cells 5,400 per cmm. May 8. Urine examination, 2,100 cc, amber, acid, specific gravity 1.025, no albumin, 15 gm (15 per cent) glucose, no acetone, no bile, no erythrocytes, no leukocytes, a few hyaline casts. Examination of the feces for blood and other pathologic elements was negative. The Wassermann reaction in the blood serum was negative. The cerebrospinal fluid contained 4 cells per cmm but no globulin by the Nonne test, and the Wassermann reaction was negative in 1 cc. May 23, the McLean index of urea excretion was 143 per cent. There were 86 mg of urea nitrogen per 100 cc of blood. May 15 the carbon dioxide tension in the alveolar air was 36 mm of mercury. Dr F B Mallory of the Boston City Hospital made the following report on the histologic examination of a piece of skin removed from the patient's arm.

The section of skin shows two types of pigment. In the lower layers of the epithelium, mainly in the basement cells, there is a fairly fine pigment of yellowish brown color, diffusely scattered through the cells. In the corium there is another pigment of a brownish yellow color which gives the typical iron reaction with the Nishimura stain for hemosiderin. This pigment is fairly abundant, especially around the coil glands and the blood vessels. It seems to be, certainly for the most part, within the cytoplasm of the connective tissue cells. Insofar as this particular tissue goes, it is indicative of a pigmentation due to an iron-containing pigment and in its distribution is

similar to what we have seen in other cases which have come to necropsy, and has all the lesions of hemochromatosis in its typical form

Progress of the Case—The patient's urine became free from sugar by limiting the diet to 30 gm of carbohydrate and 15 gm of protein. By May 22 he was able to take a diet containing 75 gm of carbohydrate, 75 gm of protein and 175 gm of fat without sugar appearing in the urine. The symptoms of sciatic neuritis disappeared. Pain developed in the upper left chest. The roentgen-ray examination showed a separation of the cartilage and bone of the first left rib, but no other pathology. Relief from this pain was not obtained until a week after the patient left the hospital. The patient's temperature varied from 98 to 99 F. On the evening of May 29 and the morning of the 30th the temperature reached 100 but by evening had fallen to 98.6. The quantity of urine usually varied from 600 cc to 1,600 cc in the twenty-four hours. May 7 it was 2,100 cc and on the 23d it was 2,600 cc.

EXPERIMENTAL FINDINGS

Analyses of the various substances made in the food, urine, feces and blood in the iron metabolism experiment are given in Table 1. During the experiment the patient ingested 10,242 cc of the food mixture and 0.9858 gm of ferric ammonium citrate. He excreted 4,260 cc of urine. The weight of the dried stools for the entire period was 161.8 gm.

The balance of nitrogen and inorganic constituents, except iron, was negative (Table 1). The patient ingested 240 mg of iron and excreted 0.192 mg in the feces. None was eliminated in the urine. The total amount of fat, the fat partition and the amounts of creatin,¹⁴ of creatinin,¹⁴ of urea nitrogen and of nonprotein nitrogen in the blood were normal. The significance of these findings will be discussed later.

The basal heat production, as determined by the method of indirect calorimetry, was obtained with the assistance of Dr. J. A. Wentworth. The experimental findings are given in Table 2.

A study of Table 2 shows that both the respiratory quotient and the heat production were normal. These findings demonstrate that there was no gross disturbance in the patient's intermediary metabolism.

SUMMARY AND DISCUSSION

Twenty per cent (0.048) of the iron ingested by the patient was not recovered in the feces. None was present in the urine. In the case reported by Howard and Stevens 85 per cent (0.0025 gm) of the iron fed was not regained. Any one explanation for the failure to completely recover the iron administered during these experiments is open to criticism. This is due to the fact that not enough is known regarding the metabolism of iron in the normal person to permit unquestionable deductions to be drawn from the findings in pathologic conditions. It is natural to expect that a certain amount of any sub-

¹⁴ Determinations made by Dr. E. A. Doisy

TABLE 1—METABOLISM EXPERIMENT, MAY 25 TO 30, 1917, ON A CASE OF HEMOCHROMATOSIS*

Substance Analyzed	Nitrogen in Gm	NH ₃ in Gm	S in Gm	P in Gm	Ca in Gm	Mg in Gm	Na in Gm	K in Gm	Fe in Gm	Cl in Gm	Fatty Acids in Mg per 100 C c	Cholesterol in Mg per 100 C c	Leucithin in Mg per 100 C c	Urea Nitrogen in Mg per 100 C c	Non protein Nitrogen in Mg per 100 C c
Whole blood									0.048†		400‡	200‡	270‡	11.0	30.0
Blood plasma											370‡	230‡	185‡		
Food	66.47		1.503	6.810	5.762	0.867	15.754	7.807	0.210	23.267					
Urine	59.00	6.30	4.835	6.561	3.734	0.597	15.172	6.505	0	16.358					
Feces	8.85		0.769	1.165	2.742	0.539	2.097	3.579	0.192						
Balance	-1.38		-1.100	-0.917	-0.715	-0.269	-1.516	-2.277	+0.018						

* Weight of patient 75 kilograms

† Milligrams per 100 c c of blood

‡ Analysis by Dr. W. R. Bloor

TABLE 2—BASAL METABOLISM, MAY 11, 1917, IN HEMOCHROMATOSIS
Patient's height, 178 cm, weight, 77.8 kg, surface area, 1.96 sq m, temperature (r), 98.4 F

Period	Percent age CO ₂ Production	Percent age O ₂ Consumption	CO ₂ Production per Minute in C c	O ₂ Consumption per Minute in C c	Respiratory Quotient	Calories per Sq M per Hr	Per Cent Below or Above Average Basal Line in Metabolism	Minute Volume in Liters	Rate of Respiration per Minute	Volume of Respiration per Minute in C c	Pulse Rate per Minute	Time of Experimental Period in Minutes
I	3.06	4.21	190	262	0.73	37.8	+0.9	6.23	17.7	352	59	9.98
II	3.06	4.14	183	216	0.71	35.7	-4.9	5.95	16.7	356	61	9.97
Average	3.07	4.18	187	254	0.71	36.8	-2.0	6.09	17.2	354	60	

stance may be lost in its passage through the body. This explanation could account for the small amount of iron not recovered in the case reported by Howard and Stevens. Gottlieb¹⁵ has shown that in dogs, subcutaneously injected iron may require a period of many days for its complete excretion. The collection of the stools for analysis in the case here reported was limited to those feces derived from the iron-containing food fed. For this reason the failure to recover all of the iron administered to this patient may have been due to a lag in its excretion. The careful studies of Queckenstedt¹⁶ have shown that all the iron administered to patients in whom there was no reason to suspect causes for the abnormal retention of that substance was not completely excreted during the period of the experiments. This observer reported the retention of considerable amounts of iron in two cases of chronic endocarditis and three cases of pernicious anemia. In these cases from 35 per cent to 51 per cent and from 8 to 35 mg of the iron fed were not again recovered during the periods of the experiments. From this discussion it is evident that the failure to recover all of the iron administered during the experiment here recorded, and in the one reported by Howard and Stevens, does not prove that there is an abnormal retention of iron in the disease, hemochromatosis. Nevertheless, it tends to support the hypothesis based on the assumption that such an abnormal retention does occur. If the latter is true, the experimental findings do not in any way show whether the fault lies in a disturbed metabolism, or in the excretory function of iron. The latter view was held by Garrod. He considered that the power of the body to excrete iron was markedly diminished. The view of Garrod is rendered untenable by the findings that the greater part of the ingested iron is eliminated in this disease.

The finding of 0.048 gm of iron per 100 cc of blood cannot be considered an abnormally large amount of that substance in the blood. Although Garrod states that 0.042 gm of iron is the maximum normal amount, Howard and Stevens show this to be erroneous.

The amount of protein in the food ingested during the metabolism experiment (Table 1) represented the minimum theoretical requirement for a normal man at rest in bed and of a body weight of 75 kg. The quantities of inorganic food elements, with the exception of iron, were somewhat less than are usually fed (Footnotes 8 and 17). The

15 Gottlieb, R. Ueber die Ausscheidungsverhältnissen des Eisens, *Ztschr f physiol Chem*, 1891, **15**, 371.

16 Queckenstedt. Untersuchungen über den Eisenstoffwechsel bei der perniziösen Anämie, mit Bemerkungen über den Eisenstoffwechsel überhaupt, *Ztschr f klin Med*, 1913-1914, **79**, 49.

17 Folin, O. Approximately Complete Analyses of Thirty "Normal" Urines, *Am Jour Physiol*, 1905, **13**, 45.

comparatively low values for the different constituents of the food ingested during the experiment probably explain the small losses of nitrogen and the inorganic substances which occurred (Table 1) If this explanation is correct, then the finding of the negative balances of the different substances studied in this experiment show that there was no disturbance in the metabolism as a result of the diseased condition, hemochromatosis This result corroborates the findings of Howard and Stevens

The studies made have failed to prove the existence of disturbances in the metabolism of the case here reported Nevertheless, from the clinical and pathologic knowledge concerning hemochromatosis it is very probable that the disease is an expression of some derangement in metabolism

CONCLUSIONS

1 A retention of food iron has been found in a metabolism experiment on a case of hemochromatosis Whether or not this retention is to be considered as abnormal is unknown Nevertheless, the hypothesis that there is an abnormal retention of iron in hemochromatosis is consistent with the experimental findings

2 The basal metabolism and the respiratory quotient, determined by indirect calorimetry, were normal These findings show that there was no gross disturbance in the intermediary metabolism

I wish to thank Dr F W Peabody for permission to carry out the respiratory metabolism experiments in his laboratory at the Peter Bent Brigham Hospital Mr A S Wetmore made most of the determinations of the inorganic elements Certain of the analyses were made in the chemical laboratory of St Luke's Hospital, Bethlehem, Pa

EXPERIMENTAL BACTEREMIA[†]J W McMEANS, M D
PITTSBURGH

A study of the effect of organisms on rabbits' appendixes when intravenously injected showed that this organ in these animals was not always the tissue most seriously attacked, and, furthermore, was never the only organ to exhibit alterations in its structure. The injection of large doses of active cultures produced a widely disseminated infection, with the development of lesions in several different organs. Although the material was selected with a view to demonstrate an elective affinity on the part of the organisms for the appendix, we were unable to determine such an affinity, even though the appendix was affected in a large number of animals. The striking feature of the experiments was the almost uniform regularity with which certain organs were attacked. Lesions were found more frequently in the stomach, lungs, skin and endocardium than in the appendix. The entire gastro-intestinal tract was commonly the seat of hemorrhages and presented this picture in the following order: stomach, appendix, duodenum, small intestine, cecum and large bowel. Hemorrhages were also noted in the thymus, muscle, pericardium, pleura, and peri-articular tissues and eye, in the order named. Almost without exception the spleen was enlarged, with tense capsule and a soft, deeply-colored pulp. Vegetative endocarditis was found in thirteen rabbits. Where there was no hemorrhage, acute lesions were found at times in the myocardium, liver, kidney and skeletal muscles. Sometimes these areas could be recognized in the gross as small yellowish foci. The joint fluid of the knees was frequently cloudy, or the synovial lining quite pink, and the organisms were recovered from these in forty-eight rabbits. Cultures made from the brain in forty-six rabbits gave eight positive results. Twenty-one of these animals showed small petechiae in the lining of the lateral ventricles, and five of the animals showed small hemorrhages in the white matter of the cord. Ten positive cultures were obtained from the gall-bladder. From this brief description it is evident that the injection of micro-organisms into rabbits' veins produced a widespread infection, and in this article we wish to discuss in detail the lesions observed.

[†] Submitted for publication, July 18, 1918[†] From the Cornell University, Surgical Division, and the Pathological Department of Bellevue Hospital

MATERIAL AND METHODS

The material for this work was selected with a view to determine the effect of organisms from certain sources on rabbits' appendixes. All of the organisms from the different materials were studied in an effort to gain information on the elective tissue affinity of organisms. The material for this work was obtained from appendixes, from the tonsils of patients having appendicitis, from several pairs of tonsils and adenoid tissue removed in the children's clinic, from tonsils of fracture patients otherwise healthy, and pus from an infected hand. Among the appendixes there were included two normal appendixes, two acute ulcerative appendixes, three acute gangrenous appendixes, three chronic appendixes, peritoneal fluid in one case of appendicitis and pus from an abscess in an abdominal incision following an operation for acute gangrenous appendicitis. The tonsils studied consisted of those from five of the patients having appendicitis, and those of thirteen patients not suffering with this disease, of the latter group, ten were from patients with fractures, but otherwise well, while the remaining three consisted of tonsils removed from children affected with chronic tonsillitis. A mass of adenoid tissue from one of the latter three was also used for culture. The details concerning the method of making the cultures is contained in the paper entitled "Experimental Appendicitis." The majority of the animals received doses varying from 15 to 75 cc of the original growth, however, at times the entire sediment from 150 cc of the original growth was injected into one animal. The individual variation in resistance among the rabbits was a marked feature, in that some of the animals which received a small dose developed a severe bacteremia with many lesions, while other rabbits inoculated with a larger dose of the same material lived, and when killed revealed but few alterations in their organs. The organisms used for these experiments included hemolytic and nonhemolytic streptococci, pneumococci, staphylococci, *B. mucosus capsulatus* and *B. coli*. Fifty-eight animals received cultures containing hemolytic streptococci, of this number there were *Streptococcus pyogenes*, 39, with *S. infrequens*, 6, with *S. anginosus*, 3, and with *S. subacidus*, 10. Forty-three rabbits treated with material containing green streptococci were divided in the following way: 32 with *S. salivarius*, 3 with *S. mitis*, 6 with *S. equinus*, and 2 with *S. fecalis*. With the streptococci it was found that rabbits inoculated with hemolytic organisms developed a more severe type of bacteremia. Twelve rabbits were treated with material including organisms of the capsulated gram-negative group of bacilli, and five received material containing *B. coli*. Six animals were injected with material from which a staphylococcus was isolated as the principal organism, while

one rabbit received an injection of a culture of pneumococci. Owing to the large dosage, most of the animals died within twenty-four hours, and those which survived the inoculation were chloroformed at varying intervals not exceeding five or six days. Of the 125 rabbits used for these experiments, eighty-one died and forty-four were chloroformed. During these experiments our attention was particularly directed to an effort to reproduce appendicitis similar to that described by Rosenow,¹ in which he attributes an elective affinity to streptococci,

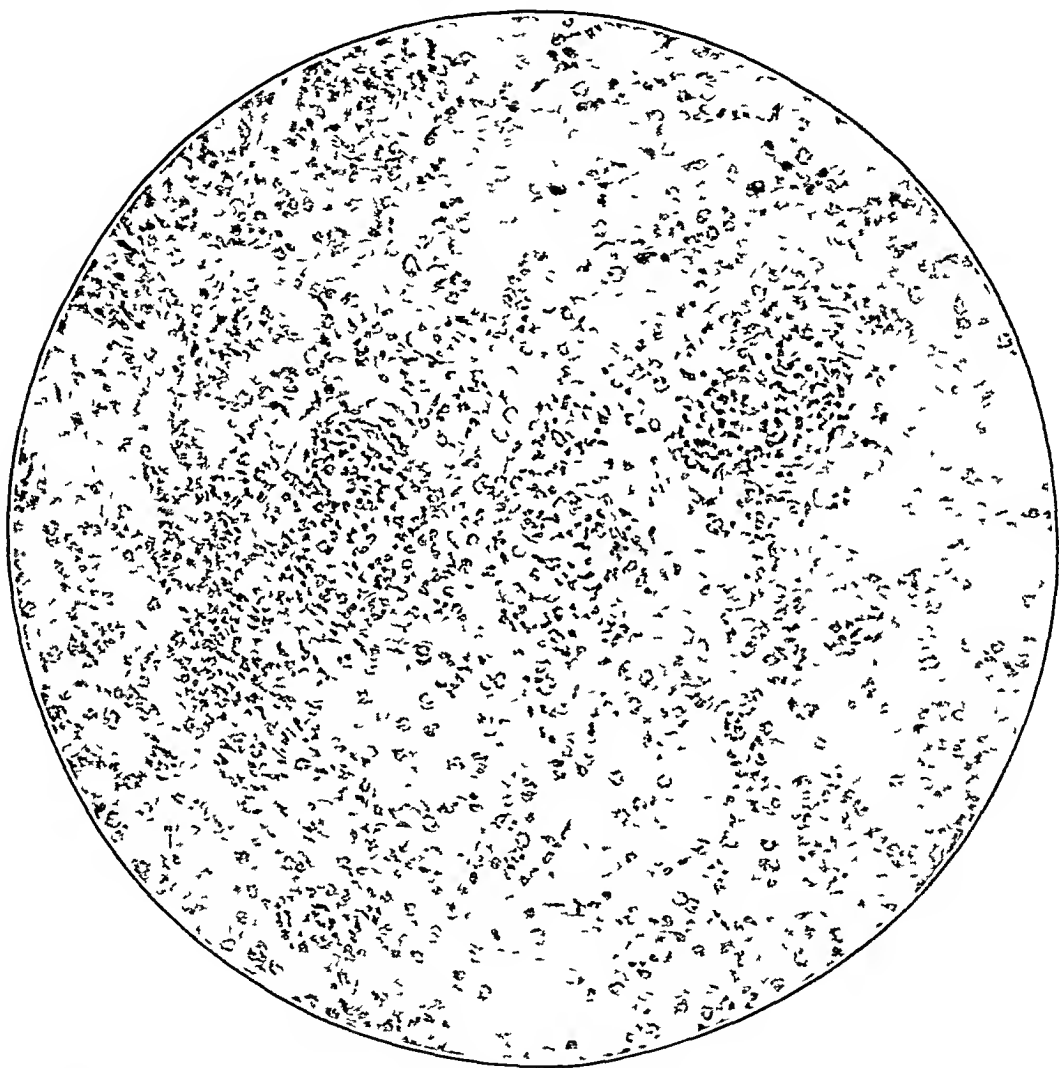


Fig 1—Animal 53, liver, *Streptococcus anginosus*, showing focal necrosis

staphylococci, and *B. coli* isolated from the teeth, tonsils or appendix in individuals suffering with this malady. Consequently, as prescribed by him, we administered large doses of the isolated organisms both from the original material and after animal passage. Routine necropsies were made on all animals as soon as death was discovered, or

¹ Rosenow Jour Infect Dis, 1912, **11**, 210, idem, Jour Infect Dis, 1914, **14**, 61

immediately on chloroforming. Cultures were made routinely from the heart's blood, knee joints and gallbladder, and sections of all the organs were fixed in Zenker's fluid and formaldehyd solution for microscopic study.

ORGANISMS STUDIED

As previously stated, all of the organisms isolated from the different sources were employed for inoculation. The sediment from each original growth was used either in whole amount or divided doses. Consequently, many of the rabbits received a mixture of organisms. At the time of inoculation, human blood agar streak plates were made in an effort to determine the nature of the organisms.

TABLE 1—

Organisms Injected	No of Animals	Stomach	Appendix	Duodenum	Small Intestine
<i>Pneumococcus</i>	1	1	0	0	0
<i>B. Friedlander</i>	1	1	1	1	1
<i>B. acid lactic</i>	10	9	8	7	9
<i>B. lactis aerogenes</i>	1	1	0	1	1
<i>B. coli communis</i>	5	5	2	3	2
<i>Staphylococcus</i>	6	3	5	3	3
Total	24	20	16	15	16

TABLE 2—PERCENTAGE OF LESIONS—

Organisms Injected	No of Animals	Stomach	Appendix	Duodenum	Small Intestine
<i>Streptococcus hemolyticus</i>	58	38 (65%)	30 (52%)	19 (32%)	17 (30%)
<i>Streptococcus viridans</i>	43	27 (63%)	16 (37%)	19 (44%)	5 (11%)
General organisms	24	20 (83%)	16 (66%)	15 (62%)	16 (66%)
Total	125	85 (68%)	62 (49%)	53 (42%)	38 (30%)

administered. After isolation from the original material, or after animal passage, pure cultures of the organisms were employed. Following the use of the original mixture, our attention was particularly directed to the streptococci contained in the original material and also those obtained from the animals at necropsy. These organisms were classified and studied according to the methods described by Holman.² Although as already stated, we were chiefly interested in the effect of

² Holman Jour Med Research, 1916, 34, 377, idem, Jour Med Research, 1916, 35, 151

the streptococci contained in the materials studied, we, nevertheless, have quite a group of animals which were injected with other types of organisms. Following this we have a number of animals which, although injected with material containing organisms in addition to the streptococci, nevertheless exhibited lesions which were quite characteristic for the streptococci.

DISCUSSION OF THE BACTERIOLOGIC RESULTS

With the administration of mixtures of organisms, varying degrees of infection were noted. Although depending in part on the dose given, it was frequently found that animals which received a small

GENERAL ORGANISMS

Heart		Joint	Muscles		Periart	Endocardium		Kidney	Thymus
Hemor	Infilt		Hemor	Infilt		Hemor	Infilt		
0	0	0	0	0	1	1	0	0	1
0	0	0	0	0	0	1	0	0	0
0	0	8	2	2	0	8	0	0	4
0	0	1	0	0	1	1	0	0	1
0	0	4	0	0	0	4	0	0	4
1	2	0	0	0	0	2	2	0	2
1	2	13	2	2	2	17	2	0	12

-SHOWING ALL TYPES OF ORGANISMS

Heart		Joint	Muscles		Periart	Endocardium		Kidney	Thymus
Hemor	Infilt		Hemor	Infilt		Hemor	Infilt		
6	10 (27%)	28 (48%)	6	3 (15%)	8 (14%)	33	3 (62%)	4 (7%)	24 (41%)
5	14 (44%)	7 (16%)	6	0 (14%)	5 (11%)	18	10 (65%)	7 (16%)	11 (25%)
1	2 (12%)	13 (54%)	2	2 (16%)	2 (8%)	17	2 (79%)	0	12 (50%)
12	26 (30%)	48 (38%)	14	5 (15%)	15 (12%)	63	15 (66%)	11 (8%)	47 (37%)

dose were more seriously affected than other animals that had received a larger dose of the same material. Another point worthy of note was the ultimate effect a certain organism or mixture of organisms had on different animals. The degree of bacteremia varied to a great extent, and the same organisms were not necessarily recovered from all post-mortem cultures of a given number of animals injected with the same material. Furthermore, in the post-mortem cultures organisms were sometimes found other than those isolated from the original material. Pneumococci and capsulated gram-negative

bacilli were found on a number of occasions where these organisms were not isolated from the original material. Although realizing the difficulty of making an absolutely correct cultural diagnosis, we feel that we are justified in emphasizing the importance of at least considering these points in a serious light and not being too hasty in believing that some organism which we found in the mixture had changed its character after injection into the rabbit's veins. Holman² has commented on the invasion of organisms from normally infected sources when animal bodies are in a lowered state of resistance. Again, different animals react differently to the same material, and we have found varying results in post-mortem cultures taken from animals injected with the same material. This variation was found in those animals which were injected with mixtures containing several organisms. Animals injected with pure cultures of the same organism did not show this variation so frequently, however, occasionally the cultures in one animal would show the organisms injected, while those in the other animal were sterile. All of the animals injected did not show a bacteremia. However, a large number of the animals died as rapid a death as those which showed organisms in the post-mortem cultures. This must undoubtedly be attributed to the severity of the toxemia produced. As previously stated, eighty-one of the rabbits died. Of this number, forty-eight rabbits had a positive blood culture at necropsy. Hemolytic streptococci were found 19 times, including *S anginosus*, 3, *S pyogenes*, 14, and *S infrequens*, 2. Green streptococci were isolated 11 times, including *S salivarius*, 7, *S mitis*, 2, and *S equinus*, 2. The *Pneumococcus* was found in the blood of one rabbit. Capsulated gram-negative bacilli were isolated 17 times, including *B Friedlander*, 3, *B acidilactici*, 12, and *B lactis aerogenes*, 2. *B coli communis* was found 5 times, *B coli communior*, 1, and *B proteus vulgaris*, 1. Six of these animals had more than one organism in the blood. Hemolytic streptococci were found in cultures from the knee joint 25 times, including *S pyogenes* 20, and *S anginosus* 5. Green streptococci were isolated 7 times, all of which were *S salivarius*. Capsulated gram-negative bacilli were obtained 14 times from the knee joint, including *B Friedlander*, 2, *B acidilactici*, 9, and *B lactis aerogenes*, 3. *B coli communis* was cultured 3 times. Cultures made from the brain in forty-six rabbits showed *S salivarius* 1 and *S pyogenes* 7 times. Cultures made from the gallbladder showed *B acidilactici*, 6, *B coli communis*, 2, *S equinus*, 1, and *B Friedlander*, 1. Along with the cultures just described, material was also taken from the pleura, pericardium and peritoneum, where these membranes showed definite signs of inflammation in the gross, with the result that a causative factor was found in most instances. Streptococci

were isolated from the appendix and glands about the cecum, as well as from the periarticular tissues and muscles. Where the organisms were not obtained in culture, they were frequently demonstrated in gram-stained sections. Thus, we found a wide dissemination of organisms in animals injected for the express purpose of demonstrating a certain elective quality for a particular tissue in these animals, with the result that lesions were found in other organs in a very appreciable percentage of cases.

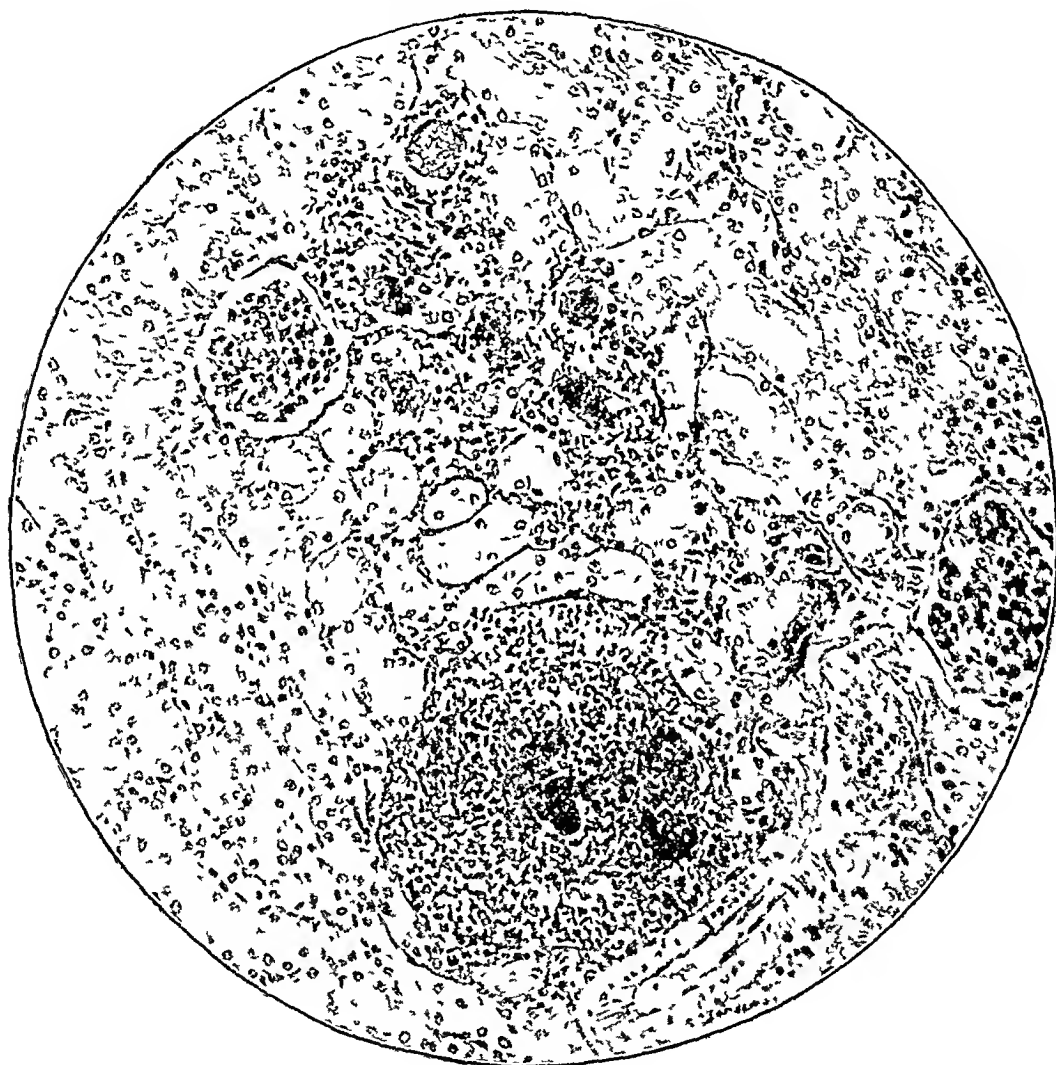


Fig 2—Animal 53, kidney, *Streptococcus anginosus*, showing embolus of cocci and glomerulus surrounded by polymorphonuclear leukocytes, endothelial cells and lymphocytes. There is also interstitial infiltration of these cells.

A survey of the bacteriologic examination of these animals indicated that in a bacteremia the organisms are quite generally distributed in all parts of the body. In case of the hemolytic streptococci, positive cultures were obtained post mortem nineteen times from the blood and twenty-five times from the knee joint. Rosenow¹ has called attention to the frequency with which hemolytic streptococci injected intravenously can be recovered from the joint cavities, a

condition which, no doubt, is the result of the interaction of two factors, the one the invasive power of the organism itself and the other, the very favorable nidus which the streptococcus finds. Green streptococci were cultivated eleven times from the blood and seven times from the knee joint. Here there is a slight advantage for the blood cultures which, no doubt, depend on the viability of the organisms, and further on the fact that green streptococci have more difficulty in attacking an uninjured tissue than do the hemolytic organisms. Of the other organisms which produced a severe reaction in the animals, the capsulated gram-negative bacilli were the most important. These organisms were isolated from the blood seventeen times and from the knee joints fourteen times.

Dick³ has commented on the apparent affinity of capsulated gram-negative bacilli for the joints. Here we must bear in mind the marked tenacity for life exhibited by these organisms and the very severe general infections which are at times observed in humans due to these organisms.

DESCRIPTION OF AND DISCUSSION ON LESIONS

The lesions observed in these experiments consisted of two types, hemorrhagic and exudative. There was a wide distribution of hemorrhages in the organs of the animals. In many animals hemorrhages were found in all parts of the body. As listed in the paper entitled "Experimental Appendicitis," the lesions which were most pronounced were those observed as hemorrhage. Hemorrhages appeared more often in the stomach, lungs, skin and endocardium than in the appendix. The gastro-intestinal tract showed hemorrhages in the following order: stomach, appendix, duodenum, small intestine, cecum and large bowel. The thymus, muscle, pericardium, pleurae, peri-articular tissues and eye showed hemorrhages in the order named. These hemorrhages were usually observed as small, discrete areas. There were at times, however, quite diffuse hemorrhages about the joints and into the muscles of the extremities as well as other of the skeletal muscles. Microscopically, they were observed as interstitial collections of blood cells, as in the muscles, while again diffuse hemorrhages were found in the follicles of the appendix. The thymus very often showed massive hemorrhage replacing the structure of parts of the gland. At times infiltration of leukocytes occurred about and through the hemorrhage. The blood vessels in the vicinity of the hemorrhage commonly showed plugs of organisms without evidence of inflammatory reaction. The protocol of Rabbit 63 will serve to illustrate the extensive character of the hemorrhagic lesions which

³ Dick Jour Infect Dis, 1914, **16**, 176, idem, Jour Am Med Assn, 1917, **68**, 622

frequently occurred. This animal was injected with the sediment from 150 c c of a twenty-four-hour growth of *B. acidilactici* obtained from an appendix. The animal died in one and one-half hours in a violent convulsion. At necropsy there were extensive bright red blotchy hemorrhages into the skin over the entire back. The conjunctiva bordering on the cornea and extending into the reflections of the bulbar conjunctiva showed many bright red hemorrhages. These varied in size from fine petechiae to quite large, irregular blotchy areas

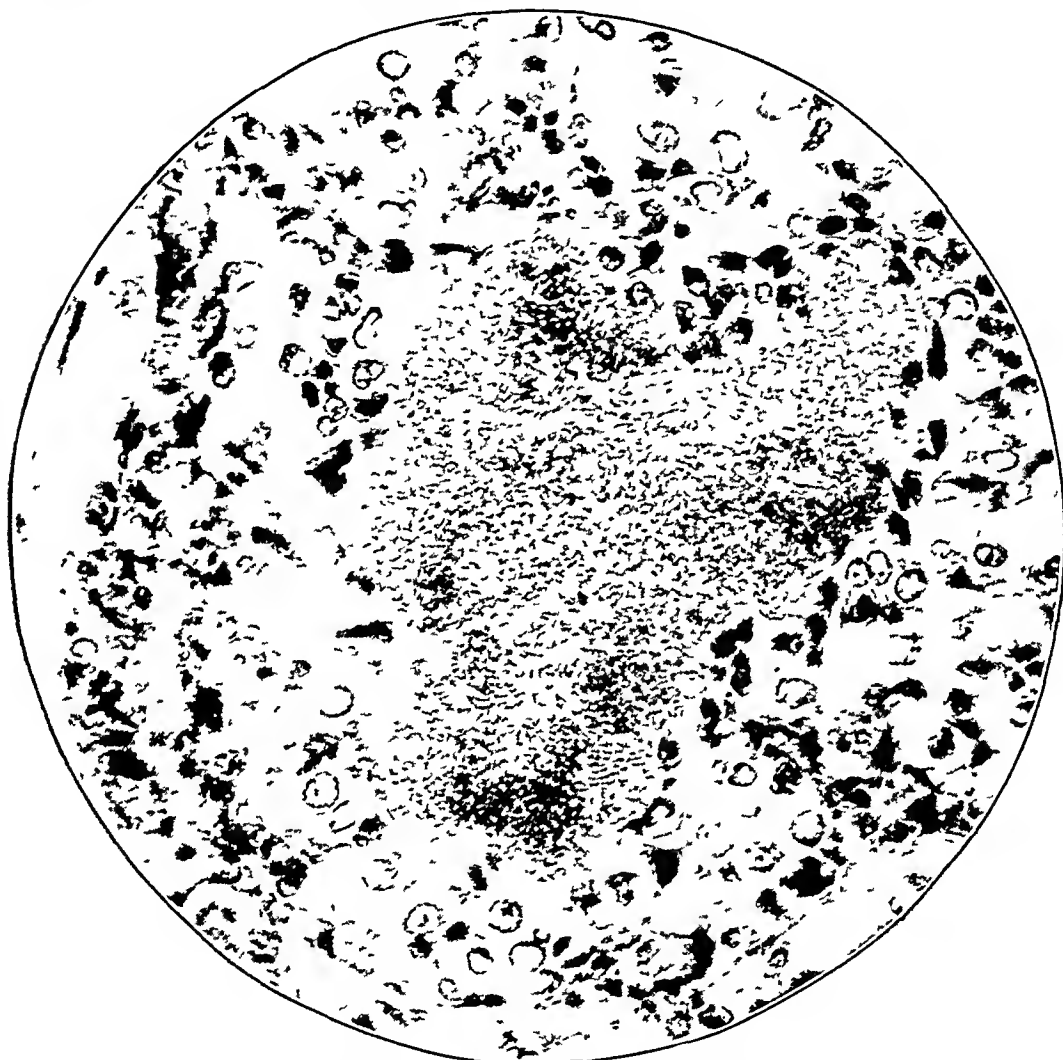


Fig. 3—Animal 64, kidney, *Streptococcus salivarius*, showing embolus of cocci in the glomerulus with an infiltration of large swollen endothelial cells

The pleural cavities were free from fluid and there were no hemorrhages into the pleura. There were, however, closely aggregated, bright red, discrete areas in the soft tissue of the anterior mediastinum, some of which were quite thick and suggested considerable leakage of blood, although there was no free blood in the mediastinal space. There was no hemorrhage into the thymus. The lungs were intensely congested and showed blotchy hemorrhages beneath the pleura. The endocardium of the left ventricle showed many discrete and confluent

bright red hemorrhages. The omentum contained many bright red hemorrhages. Some of these were blotchy, while others were very prominent and formed small blood blisters. These hemorrhages measured from 0.2 to 0.5 cm in diameter. There were a few bright red hemorrhages into the mesentery. The stomach showed several small chocolate colored areas in the mucosa of the cardia. These did not appear to be of recent origin. In the first half of the duodenum there

TABLE 3—

Organisms Injected	No of Animals	Stomach	Appendix	Duodenum	Small Intestine
<i>S. pyogenes</i>	28	19	15	7	5
<i>S. subacidus</i>	10	5	2	2	1
<i>S. anginosus</i>	3	3	1	1	1
<i>S. infrequens</i>	2	1	1	1	0
<i>S. pyogenes</i> — <i>S. salivarius</i>	5	3	3	2	3
<i>S. pyogenes</i> — <i>pneumococcus</i>	6	4	5	4	3
<i>S. infrequens</i> — <i>B. Friedlander</i>	4	3	3	2	4
Total	58	38	30	19	17

TABLE 4—

Organisms Injected	No of Animals	Stomach	Appendix	Duodenum	Small Intestine
<i>S. salivarius</i>	31	19	13	13	4
<i>S. equinus</i>	6	4	2	3	0
<i>S. fecalis</i>	2	2	0	2	0
<i>S. mitis</i>	3	1	1	1	1
<i>S. salivarius</i> — <i>S. equinus</i>	1	1	0	0	0
Total	43	27	16	19	5

was no change. However, from here on there was a diffuse speckling of the bowel with purpuric spots. These were visible equally well from the serosa and mucosa. In the midportion of the ileum there was an area of hemorrhage into the wall measuring 0.5 cm in diameter. There were many smaller pinpoint-sized areas scattered diffusely in the bowel wall. Peyer's patches were markedly involved, presenting diffuse areas of hemorrhage which extended deep into their substance. There was a diffuse speckling of the cecum just beyond the ileocecal valve. The appendix mucosa was peppered over with a great number of small discrete and confluent hemorrhages which were just beneath

the mucosal surface The large bowel and upper rectum showed several areas of hemorrhage in the mucosa All of the animals injected with *B lactis aerogenes* and *B acidilactici* showed a similar picture, although Rabbit 63 was the only animal which died so rapidly Although microscopically these hemorrhages were observed either as interstitial or more diffuse infiltrations of red cells which replaced tissue, there were, nevertheless, occasionally inflammatory infiltrations

—STREPTOCOCCUS HEMOLYTICUS

Heart		Joint	Muscles		Periart	Endocardium		Kidney	Thymus
Hemor	Inflt		Hemor	Inflt		Hemor	Inflt		
4	9	14	2	2	2	15	1	8	9
0	0	4	0	0	1	2	0	0	3
0	1	0	1	0	1	2	0	1	2
0	0	0	1	1	0	1	1	0	0
0	0	4	1	0	2	2	0	0	3
2	0	4	1	0	1	6	0	0	4
0	0	2	0	0	1	4	1	0	3
6	10	28	6	3	8	33	3	4	24

—STREPTOCOCCUS VIRIDANS

Heart		Joint	Muscles		Periart	Endocardium		Kidney	Thymus
Hemor	Inflt		Hemor	Inflt		Hemor	Inflt		
4	13	7	5	0	4	13	6	6	9
1	1	0	1	0	1	2	1	1	1
0	0	0	0	0	0	1	0	0	1
0	0	0	0	0	0	1	2	0	0
0	0	0	0	0	0	1	1	0	0
5	14	7	6	0	5	18	10	7	11

With the streptococci, hemorrhage was a constant feature which was more marked with the hemolytic streptococci Here, however, in contradistinction to the animals treated with capsulated gram-negative bacilli, exudative lesions were more apt to occur Although very often the latter lesions were not discovered except by microscopic examination, they were, nevertheless, very clearly seen in the gross in some animals Rabbit 157 was injected with the sediment from 75 c c of a twenty-four-hour growth of *Streptococcus pyogenes* Five days later the animal was very sick and was chloroformed and necropsied immediately There were yellowish white streaks in most of the skeletal

muscles These were observed as tiny spinales running in the direction of the muscle fibers They were compact and no material could be squeezed from them On cross section they were seen as small round yellowish dots The same type of nodules were found diffusely scattered through the heart muscle and kidney There was a pea-sized warty nodule of yellow fibrin on the mitral valve which almost closed the opening Fading pinkish red areas were found in the mucosa of the small intestine and appendix *Streptococcus pyogenes* was isolated from the muscle Rabbit 64 was injected with the sediment from 150 cc of a twenty-four-hour growth of *Streptococcus salivarius* Two days later the animal died Necropsy was performed at once There were blotchy hemorrhages into the skin of the back and sides Circumscribed, deeply-colored areas were found in the lungs as well as blotchy hemorrhages into the pleura The heart showed some small petechiae in the pericardium, with many tiny pinpoint white dots shining through Similar small dots could be seen through the endocardium and on section they were observed as millet-like bulging masses on the cut surface They were solid and no material could be squeezed from them There was a warty fibrinous deposit on the tricuspid valve The stomach showed many fine petechial dots in the mucosa of the cardiac end A similar condition was noted in the first part of the duodenum and also in the appendix The kidneys showed a very marked bright red streaking of their cortexes The intermediate zone was deeply congested and irregular in outline There were many tiny white dots distributed throughout the cortex and for some distance into the medulla These were similar in appearance to the foci observed in the heart muscle *Streptococcus salivarius* was isolated from the heart blood and knee joint Although these two animals were injected with different members of the streptococcus group, the distribution of the lesions was quite similar, save for the muscle, and microscopically these foci had much in common These lesions will be described in detail later with special reference to the animals and ones showing similar lesions

One hundred and one animals were injected with streptococci Exudative lesions were observed in the heart twenty-four times, in the kidney eleven times and in the muscle three times Of the rabbits which showed a myocarditis, 13 received *S salivarius* and 10 *S hemolyticus*, including *S pyogenes*, 9, and *S anginosus*, 1 One rabbit was treated with *S equinus* The two rabbits injected with staphylococci showed abscesses in the myocardium Changes noted in the kidney were divided in the following way 6 with *S salivarius*, 1 with *S equinus* and 4 with *S hemolyticus*, including *S pyogenes*, 3, and *S anginosus*, 1 The skeletal muscle lesions were produced twice by

S. pyogenes hemolyticus and once by *S. hemolyticus infrequens*. There were two other rabbits which showed exudative muscle lesions, both of which were injected with *B. acidilactici*. However, in gram-stained sections, both of these lesions showed gram-positive cocci in the neighboring vessels. Of the animals injected with streptococci, seven showed exudative lesions in both the heart and kidney, while one of these showed lesions in heart, kidney and muscle. The latter animal was

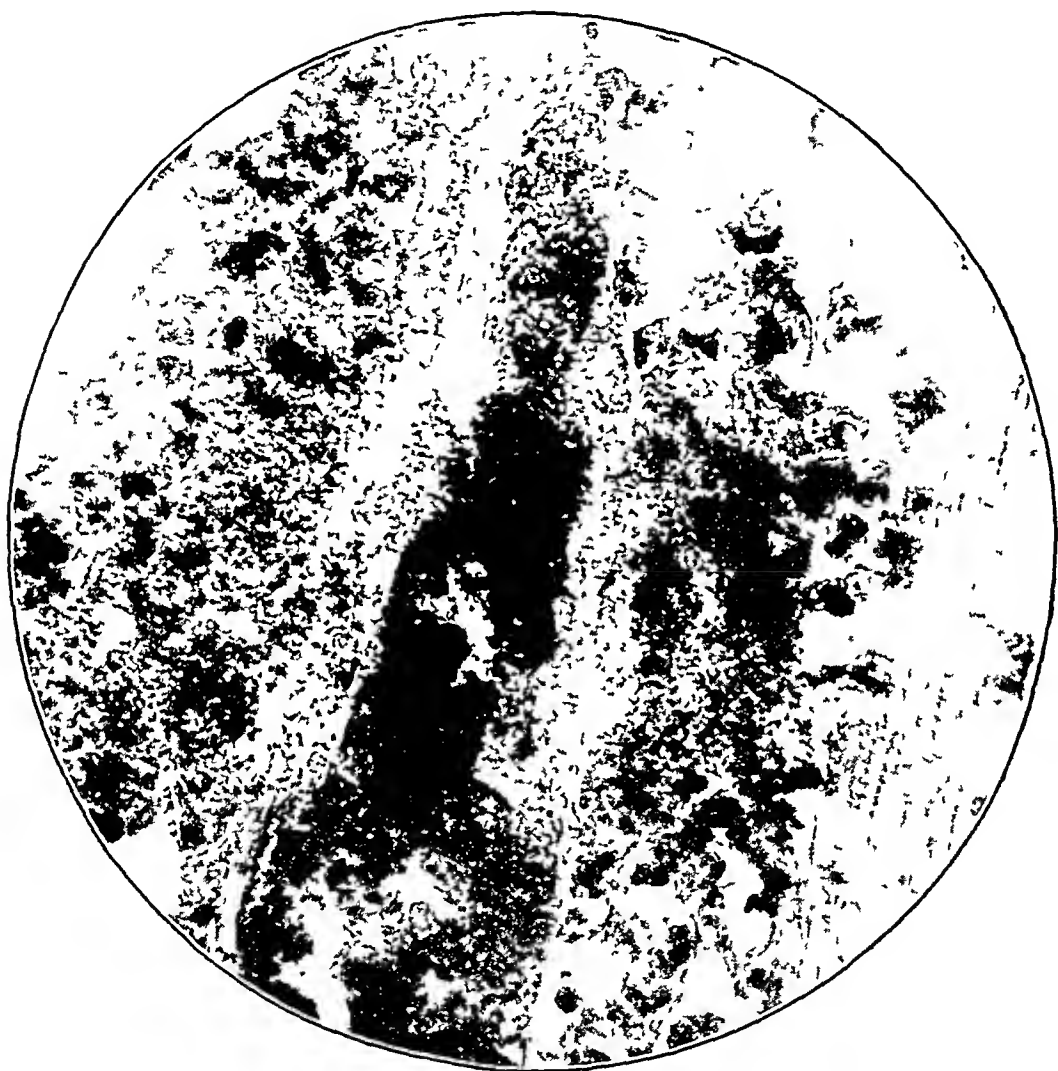


Fig. 4—Animal 64, heart muscle, *Streptococcus salivarius*, showing embolus of cocci surrounded by large swollen endothelial cells, some of which contained phagocytized cocci

inoculated with *S. pyogenes*. Of the remaining 6 which showed lesions in both heart and kidney, 4 received *S. salivarius*, while the other 2 were inoculated, respectively, with *S. anginosus* and *S. pyogenes*. As previously stated, the prominent features observed in these animals was the occurrence of discrete or confluent hemorrhages. The size of the doses given caused a rapid death of most of the animals, while the remaining members of individual groups were chloroformed either at

the time or within a day or two for comparison. The high percentage of hemorrhage observed in our animals corresponds closely to the results of Rosenow, who believes such hemorrhages are the forerunners of exudative lesions. In our animals the hemorrhages occurred in the majority of cases without evidence of inflammatory infiltration. Small vessels in the vicinity of these areas were frequently found plugged with cocci or bacilli, apparently without damage to the vessel as far as evidenced by an inflammatory reaction. The effect of the toxins of the organisms on the capillary walls must be an important factor. However, from the foregoing evidence the mechanical effect of these plugs on the vessel walls must also be a point of first importance. When the amount of sediment given is considered, the rabbit has received a considerable bulk of foreign matter into his vessels, which, no doubt, has a decided damaging effect on delicate capillary structures, apart from the injury done by the activity of the organisms and their toxins. We believe, however, that the large doses employed caused an overwhelming infection which was evidenced in the main by a fairly constant distribution of hemorrhages in the several parts of the animal's body.

Heart Valves—Thirteen rabbits showed vegetative lesions and in two others the valves contained small discrete hemorrhages. Deposits of fibrin were found on the mitral and on the tricuspid valve, each six times. In one rabbit vegetative lesions were found on both the mitral and tricuspid, while in the last case there was a mural vegetation in the right ventricle. Eight of these rabbits were injected with green streptococci, including *S mitis*, 2, *S salivarius*, 5, and *S equinus* and *salivarius*. Two received injections of hemolytic streptococci, 1 *S pyogenes*, and the other *S infrequens*. Of the remaining three, two were given staphylococci and the third *B acidilactici*. Of the two rabbits exhibiting hemorrhage into the valves, the first was inoculated with *S salivarius* and the second with *S equinus*.

Endocarditis has been produced by a variety of organisms, and it is generally known that the production of the lesion is associated with infection. Fulci⁴ was unable to produce an ulcerative or vegetative endocarditis by using sterile toxins, even when associated with mechanical or chemical injury. This observation was in accordance with the work of Rosenback,⁵ done years before, who said that mechanical injury did not of itself produce inflammatory changes in the valves. So, as Orth⁶ has pointed out, the presence of micro-organisms circulating in the blood is essential for the production of the condition.

4 Fulci Ziegler's Beitr z path Anat u z allg Path, 1908, **44**, 349

5 Rosenback Arch f exper Path u Pharmacol, 1878, **9**, 1

6 Orth Virchows Arch f path Anat, 1886, **103**, 300 and 333

About this same time Ribbert⁷ succeeded in producing endocarditis by injecting emulsions of potato and staphylococci. However, since this time, many other workers have succeeded in producing endocarditis without first causing injury to valves. Saltykow⁸ succeeded by using cultures of *Staphylococcus pyogenes aureus*. Lissauer⁹ found endocarditis in two of twenty rabbits which received injections of a coccus

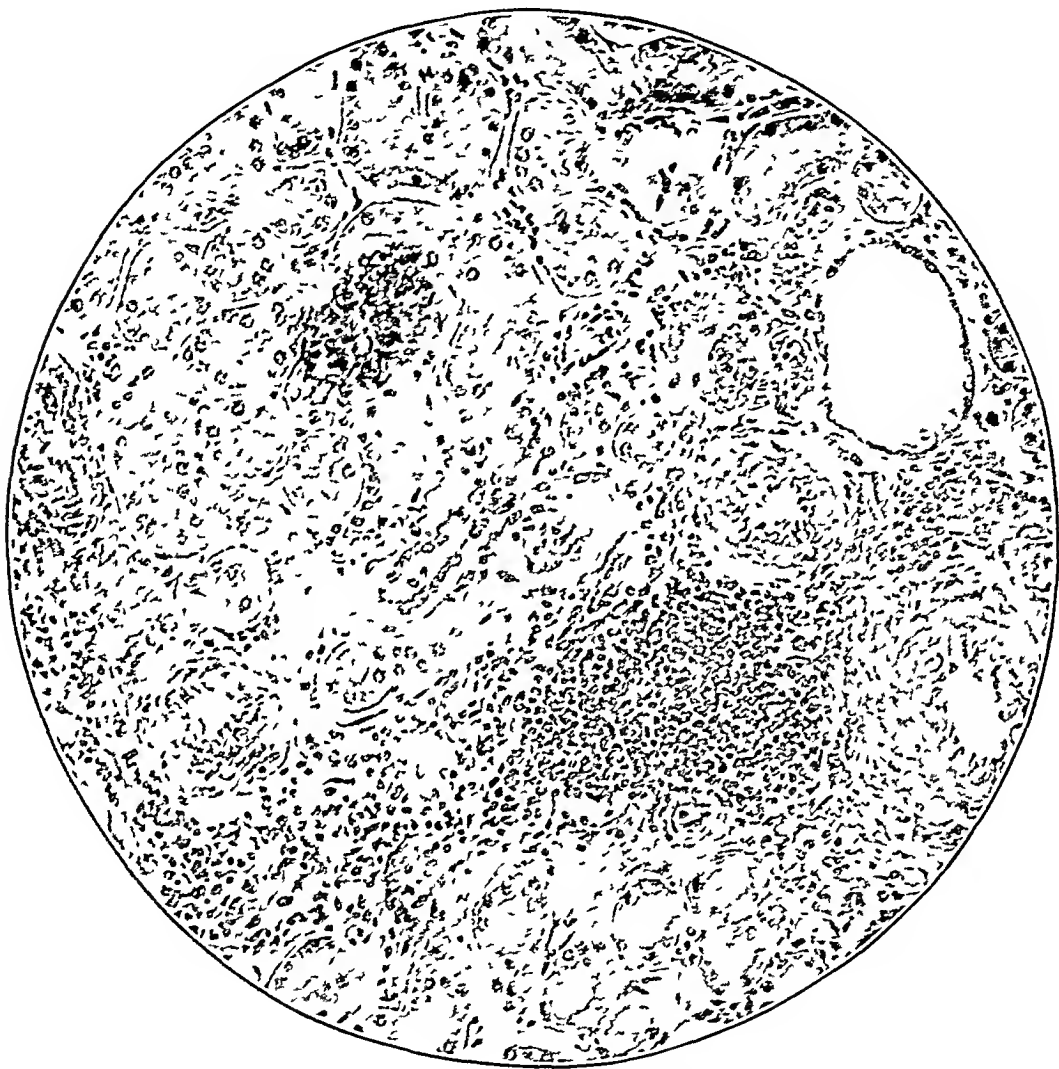


Fig 5—Animal 116, kidney, *Streptococcus equinus*, showing dense interstitial infiltration of lymphocytes

like *Staphylococcus albus*. Of the various organisms associated with endocarditis, streptococci are the most frequent. However, other organisms are found often enough to be given worthy consideration. In forty-three cases of infectious endocarditis, Harbitz¹⁰ found 7 streptococci, 5 pneumococci, 8 staphylococci, 3 not classified and 10 healed

7 Ribbert Fortschr d Med, 1886, 4, 1

8 Saltykow Virchows Arch f path Anat, 1912, 209, 126

9 Lissauer Centralbl f Path, 1912, 23, 243

10 Harbitz Deutsch med Wchnschr, 1899, 121.

In the human, infectious endocarditis due to streptococci has been described by a number of authors. Poynton and Paine¹¹ concluded that the endocarditis in rheumatism is due to the organisms of rheumatism, and that the tonsils in rheumatic cases harbor the *Micrococcus rheumaticus*. Libman¹² has described a type of subacute bacterial endocarditis and he and Cellar have described in detail the organism associated with this disease. Osler,¹³ Schottmuller¹⁴ and Horder¹⁵ have described a similar type of disease. Billings¹⁶ in a report of 14 cases of infectious endocarditis found pneumococcus 11 times and streptococci 3 times. The findings coincide with the belief of Rosenow, who is convinced that the organisms responsible for endocarditis are modified pneumococci, which readily form clumps, thus facilitating the production of emboli, which is the primary step in endocarditis according to his interpretation. Experimentally, streptococci have been employed by many authors for the production of endocarditis in laboratory animals. Beattie¹⁷ produced endocarditis and polyarthritis in animals injected with *Micrococcus rheumaticus*. These observations have been substantiated by the work of Poynton and Paine,¹⁰ Cole,¹⁸ Walker,¹⁹ Libman and Cellar,¹² and others. Horder¹⁵ found that streptococci cultivated from the blood in cases of chronic infectious endocarditis, as well as allied streptococci cultivated from the throat and feces, are prone to produce endocarditis in animals. Rosenow found that streptococci isolated from cases of endocarditis showed a special affinity for the endocardium of laboratory animals. He found that animals injected with these organisms gave 84 per cent endocarditis as against only 14 per cent in animals inoculated with streptococci from other sources. Further than this, the disease was always an embolic process and was caused by modified pneumococci. As against these results, Henrici²⁰ concluded that streptococcal endocarditis usually develops by implantation on the surface of the valve. The latter author observed no specific difference in the affinities of the various

11 Poynton and Paine. Lancet, London, 1910, **178**, 1524

12 Libman. Tr Assn Am Phys, 1910, **25**, 5. Libman and Cellar. Am Jour Med Sc, 1910, **140**, 516

13 Osler. Brit Med Jour, 1885, **1**, 467, 522, 577 and 607, idem, Practitioner, London, 1893, **50**, 183

14 Schottmuller. Munchen med Wchnschr, 1903, **50**, 849 and 909, 1910, **57**, 617

15 Horder. Quart Jour Med, 1908-1909, **2**, 289

16 Billings. THE ARCHIVES INT MED, 1909, **4**, 409

17 Beattie. Jour Med Research, 1906, **14**, 399, idem, Edinburgh Med Jour, 1908, **13**, 391

18 Cole. Jour Infect Dis, 1904, **1**, 714

19 Walker. Brit Med Jour, 1907, p 1233

20 Henrici. Jour Infect Dis, 1916, **19**, 572

classes of streptococci for the heart valves. Fox²¹ inoculated rabbits with a freshly isolated strain from the tonsil of a girl with rheumatism, four times in twenty days and found fibrinous mitral endocarditis, also myocarditis. This author also gave a rabbit eight doses of a streptococcus pyogenes from a case of puerperal sepsis and found mitral endocarditis as well as myocarditis. He concluded that all cases of valvular disease have primary myocarditis present at the base of



Fig 6—Animal 120, heart muscle, *Streptococcus salivarius*, arteriole in heart muscle showing acute endarteritis with puffing of the intima and infiltration of endothelial cells, lymphocytes and leukocytes

the valve, and that this condition leads to an edema of the valve which permits of endocarditis.

The lesion observed on the valves of our animals consisted either of subendothelial hemorrhages or vegetations. Microscopic examination of the latter structures showed masses of cocci surrounded by fibrin with dense collections of leukocytes and lymphocytes. The endothelial covering of the valve was missing where the vegetation was

21 Fox Centralbl f Path, 1913, 24, 529

adherent and fibrin and inflammatory cells with red blood cells extended into the deeper layers of the valve. In one case a small nodule near the edge of the valve closely resembled the lesions observed beneath the mural endocardium, which are described under heart muscle. Aside from the changes described subendocardial hemorrhages were found in sixty-eight animals.

Heart Muscle—In acute rheumatic fever there is a type of myocarditis which is considered as specific for infection with the rheumatic virus. These bodies have been termed Aschoff-Geipel bodies and are most commonly noted in the walls of the left ventricle beneath the endocardium and pericardium and also frequently about the bases of the valves. These areas were first described by Aschoff,²² who found that there was a proliferation of cells arranged in the form of a fan or rosette, making up nodules which occurred near the small or medium sized vessels, and often in close relation to the adventitia of these vessels. The lesions consist of large cells which have one or more polymorphous nuclei and the center of the nodule is faintly staining as if composed of necrotic masses of protoplasm. Beside the so-called giant cells, the lesions include large and small lymphocytes, with the latter more numerous at the periphery. These bodies have since been described by Wachter,²³ Thorel,²⁴ Coombs,²⁵ Fraenkel,²⁶ Douglas,²⁷ Low,²⁸ Thalheimer and Rothschild,²⁹ and many others. Closely allied or similar lesions have been produced experimentally by a number of workers. Bracht and Wachter³⁰ observed submiliary nodules in three or four cases giving a rheumatic history. *S. mitis* was isolated from the heart's blood in two of the cases, and when this organism was injected into rabbits they failed to find Aschoff bodies in the hearts of the rabbits. They found, however, a focal myocarditis which consisted of patchy lymphocytic infiltration. They considered these results significant, however, in that rabbits inoculated with *S. pyogenes* showed miliary abscesses in the heart muscle. Jackson³¹ compares the nodules produced experimentally with those found in human rheumatic hearts. This author inoculated rabbits with a hemolytic streptococcus which was obtained from a milk borne epidemic of sore throat. The myocar-

22 Aschoff Verhandl d deutsch, path Gesselch, 1904, 8, 46

23 Wachter Munchen med Wchnschr, 1908, 55, 1101

24 Thorel Lubarsch Ostertag, 1915, 17, 435

25 Coombs Jour Path and Bacteriol, 1911, 15, 490, idem, Lancet, London, 1909 1, 1377

26 Fraenkel Ziegler's Beiz z path Anat u z allg Path, 1912, 52, 597

27 Douglas Jour Path and Bact, 1913, 18, 119

28 Low Ziegler's Beiz z path Anat u z allg Path, 1910, 49, 1

29 Thalheimer and Rothschild Jour Exper Med, 1914, 19, 417, and 444

30 Bracht and Wachter Deutsch Arch f klin Med, 1909, 96, 493

31 Jackson Jour Infect Dis, 1912, 11, 243, 1913, 12, 364

dium contained small groups of cells which were quite uniformly distributed and occupied the space between one or more muscle fibers with the long axis parallel to the fibers. The most conspicuous cell in these areas was large, with large oval or round and sometimes irregular nuclei. These large cells often contained phagocytosed streptococci. In addition to the larger cells, there were smaller cells with more deeply stained nuclei and a small amount of cytoplasm. These cells and a few



Fig 7—Animal 148, skeletal muscle, *Streptococcus infrequens*, showing hemorrhage

leukocytes were irregularly disseminated throughout the area. Thalheimer and Rothschild²⁹ injected rabbits with streptococci from epidemic sore throat and had seven animals develop the usual pyogenic type of lesions caused by *S. pyogenes*. Along with an extensive degeneration and destruction of muscle associated with a leukocytic infiltration, mainly polymorphonuclear and great numbers of cocci, there were a few fusiform areas resembling somewhat those described by Jackson. There were no giant cells, however, and no typical Aschoff bodies.

They base their belief on the fact that the cells were not basophilic and that their protoplasm did not stain red with methyl-green pyronin. These same authors also treated rabbits with *S. mitis* and *S. rheumaticus* (Poynton and Paine) and found no evidence to indicate that the focal myocarditis produced was similar to the submiliary nodules of Aschoff. In two rabbits inoculated with *S. viridans*, Hartzell and Henrici³² found proliferative lesions in the heart in which multinucleated giant cells were prominent, and which they believed were similar to Aschoff-Geipel bodies. In a later paper, Henrici²⁰ described lesions which in the general appearance of the cells, their basicity, their accumulation in fusiform masses between the muscle fibers, or in rosettes about the vessels, their frequent subendocardial position and the frequent occurrence of multinucleated giant cells, presented all the characteristics of the typical Aschoff-Geipel nodules. This author also found no difference in the affinity of hemolytic and nonhemolytic streptococci for the heart muscle.

The reactions in the heart muscle of our animals varied somewhat in that the changes noted did not always consist of the same type of cell reaction. In some of the specimens leukocytic infiltration formed the prominent feature, while in other specimens there was a proliferation of large endothelial cells. At times these changes were noted independently or in combination in the same specimen. Where the leukocytic infiltration was the main feature, there was invasion of these cells between the muscle fibers, plugging the small capillaries and lymph spaces, forming a patchy interstitial inflammation. At times the small arterioles presented an acute endarteritis with a puffing of the intima and an infiltration of inflammatory cells inside of the elastica interna. When the reaction advanced the bordering muscle cells were invaded, with the formation of multiple small abscesses throughout the heart muscle. These areas consisted either of dense collections of leukocytes or of necrotic masses surrounded by a zone of these cells. Areas of a light to deep blue granular material were at times seen replacing the heart muscle. These areas were frequently unattended by an inflammatory reaction and involved irregular sections of the muscle fibers. These were looked on as areas of calcification, in that a number of preparations took the silver nitrate stain. Masses of cocci were frequently found in the center of the foci described above. Where *S. salivarius* was used, another type of reaction was the rule. In many areas lymphocytes were the predominant cell, with a few leukocytes scattered throughout, while again small and large mononuclear cells were in greater numbers. At times rather large cells were arranged about the blood vessels and in small nodules beneath the endocardium.

32 Hartzell and Henrici Jour Am Med Assn, 1915, **64**, 1055

and about the bases of the valves. There was also a similar type of proliferation which at times took place about the necrotic areas. Where clumps of cocci occurred in these areas, they were often phagocytosed by the surrounding cells. These cells were swollen or elongated, with deep staining round or irregular nuclei. The protoplasm of these cells was wide, with a marked tendency to basophilia. However, many cells had a fairly light protoplasm, with a more dis-

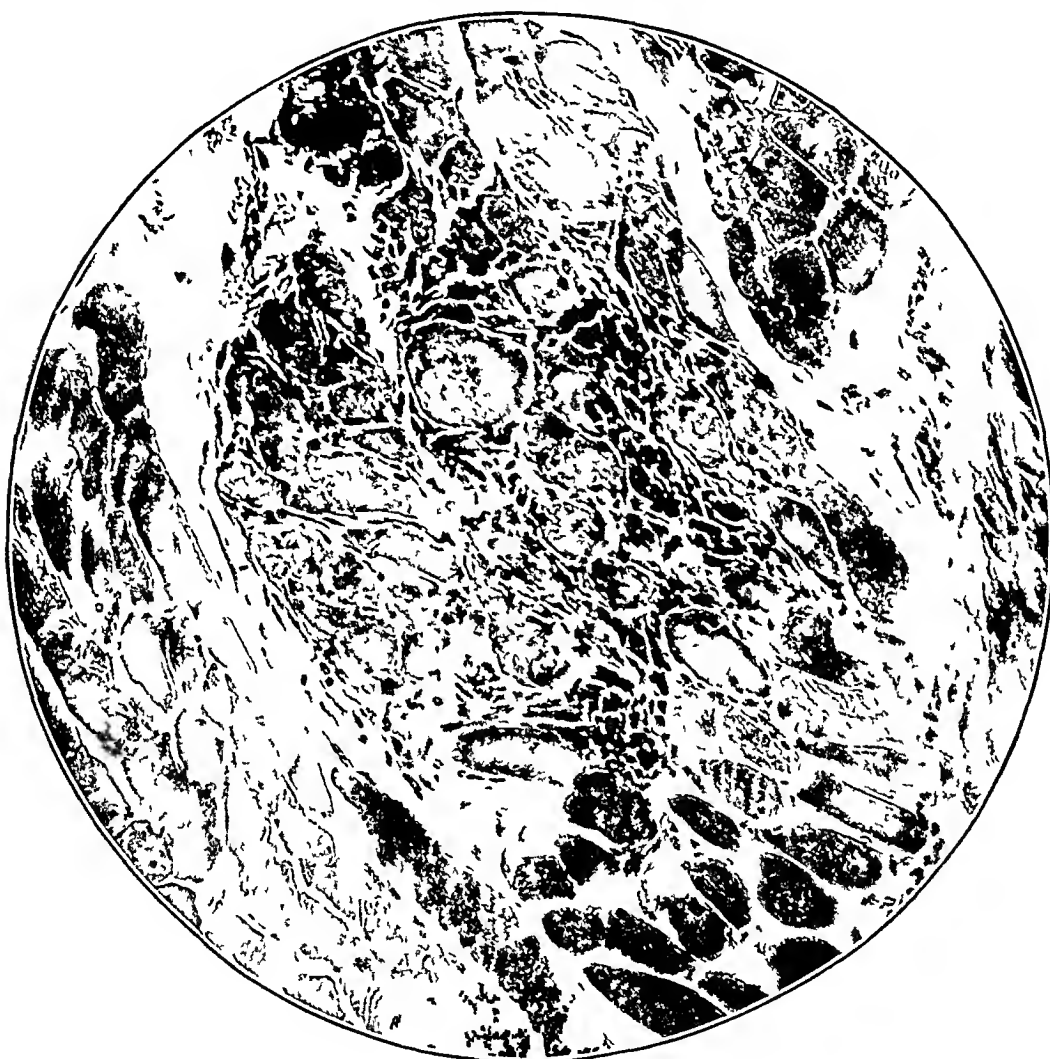


Fig 8—Animal 157, skeletal muscle, *Streptococcus pyogenes*, showing an exudative lesion consisting of endothelial cells, lymphocytes and a few polymorphonuclear leukocytes

tinctly outlined nucleus, and in these, occasional nuclear figures were observed. Besides the lesions described, which were found in the rabbits injected with streptococci, hemorrhages were observed in twelve animals where there were no such lesions. The hemorrhages were found most commonly within the papillary muscles of the left ventricle. Table 2 shows the number of animals affected as well as the organisms used.

Joints—Arthritis has been produced experimentally in animals by a number of investigators Wassermann³³ isolated a diplococcus which he regarded as specific for rheumatism Poynton and Paine¹⁰ confirmed this view Beattie¹⁷ found that *Micrococcus rheumaticus* caused nonpurulent arthritis in 60 per cent of the rabbits, and that these organisms differ from ordinary streptococci in this respect Beattie and Yates³⁴ found that ten out of thirty-five strains of *S viridans* isolated from various sources produced arthritis in rabbits This was observed chiefly in the hind legs Rosenow² isolated three types of streptococci in rheumatism, each of which could be readily converted into the other These organisms produced arthritis in a small percentage and endocarditis in a high percentage of animals The results of Thalheimer and Rothschild²⁹ are directly opposed to these, in that these authors found 50 per cent arthritis and 7 per cent endocarditis in animals injected with *S mitis* Furthermore, 45 per cent of eleven animals injected with *S rheumaticus* had arthritis These authors also found a variation in the ability of strains to produce arthritis, and concluded that the deduction of a distinct variety of species of streptococcus based on the power to cause arthritis in rabbits is unwarranted Jackson³¹ found no histologic differences in the joints of rabbits injected with various streptococci Henrici²⁰ found that joint lesions were produced with equal frequency by both hemolytic and nonhemolytic strains Schloss and Foster³⁵ used a hemolytic streptococcus from a throat and produced an arthritis suggestive of rheumatic arthritis These authors asserted that chronic arthritis developed after repeated injections of this organism Coombs, Miller and Kettle³⁶ produced proliferative lesions in the joints of rabbits inoculated with *S rheumaticus* Jackson³¹ and Koch³⁷ have noted similar alterations in rabbits inoculated with a variety of streptococci Dick³ has twice reported the production of arthritis in rabbits and dogs with *B lactis aerogenes* This author also found that capsulated gram-negative bacilli isolated from the joints of persons suffering with rheumatoid arthritis showed a higher degree of affinity for the joints in animals The arthritis varied from an acute hemorrhagic inflammation to a chronic deforming arthritis In the more chronic cases the leukocytes present in the exudate were mostly of the round cell type Rosenow has called attention to the frequency with which capsulated gram-negative bacilli are found in the joint cavities of animals injected experimentally with these organisms

33 Wassermann Berl klin Wchnschr, 1899, **36**, 638

34 Beattie and Yates Jour Path and Bacteriol, 1913, **17**, 538

35 Schloss and Foster Jour Med Research, 1913, **29**, 9

36 Coombs, Miller and Kettle Lancet, London, 1912, **2**, 1209

37 Koch Ztschr f Hyg Infectiouskr, 1912, **72**, 321

Routine examination of the knee joints was conducted in all rabbits. Sections of the synovial membrane of the joints were not made. Cultures were made from all cases, and the joint fluid examined in a sufficient number of animals to determine the character of the exudate. The joint cavities were frequently distended with a thick, turbid, mucoid fluid, which, on examination, contained leukocytes, fibrin and bacteria. In case of infection with capsulated gram-negative bacilli,

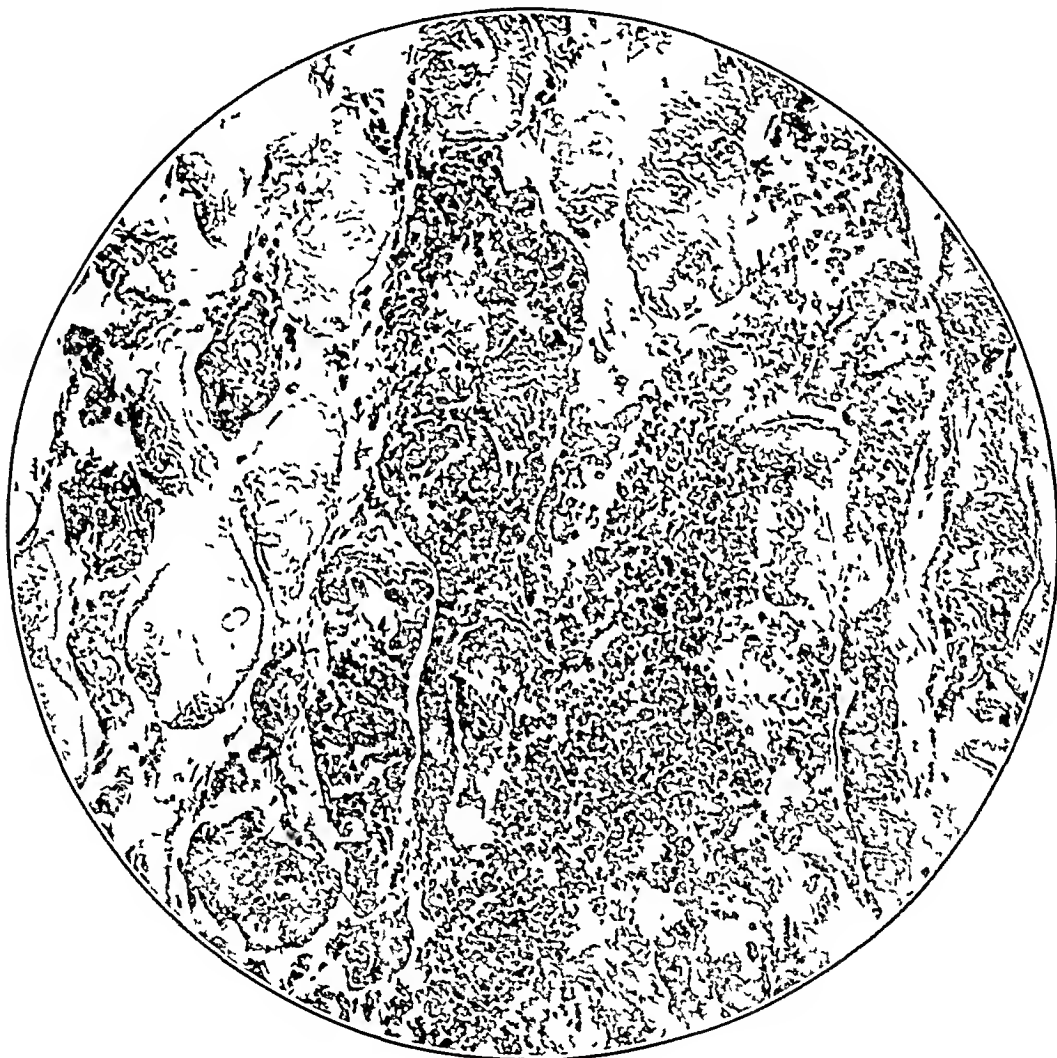


Fig 9—Animal 157, skeletal muscle, *Streptococcus pyogenes*, showing marked destruction of muscle cells with a more acute reaction

the joint fluid was frequently very sticky and stringy. In many animals the only sign of joint involvement was reddening of the synovial covering, or tiny petechiae into this membrane. Periarthritic hemorrhages occurred in fifteen rabbits. Eight were due to hemolytic streptococci, five to *S. viridans*, one to *Pneumococcus* and one to *B. lactis aerogenes*. Hemolytic streptococci were isolated twenty-five times from the joint cavity and *S. viridans* seven times. Fourteen of fifteen animals injected

with capsulated gram-negative bacilli from several sources not including joints showed these organisms in the joints at necropsy. *B. coli communis* was found four times. All of the animals used received very large doses and lived only a day or so following the injection. Consequently, sufficient time had not elapsed for the development of varying degrees of reaction. We observed these conditions in the acute stage, and as a whole, found very little difference in the picture presented. From these results it would appear that the joint in an overwhelming infection is frequently the subject of attack by various organisms causing such infections.

Voluntary Muscles—Rosenow² isolated streptococci from cases of muscular rheumatism in man and was able to reproduce similar lesions experimentally in animals by using the particular streptococci. Recently Henrici has reported the production of lesions in the voluntary muscles of rabbits by injecting them intravenously with various strains of streptococci.

The lesions observed in the muscles of our rabbits were of two kinds, either interstitial hemorrhages or areas of infiltration and necrosis, with, at times, areas of proliferative reaction. The first type was observed usually as small, well defined bright patches of hemorrhage. In several instances, however, the hemorrhage was very diffuse and in several rabbits involved all the muscles of an extremity. In the areas of necrosis with exudate, the muscle fibers were fragmented and formed hyaline-like granular bands. There was infiltration of lymphocytes and leukocytes with clumps of cocci in the neighboring vessels. At times there was an endothelial-like proliferation in the spaces between the muscle fibers. In one specimen these cells were arranged in and out among the muscle fibers in a wavelike or sweeping fashion. These cells varied in size and shape. Some were large, with large vesicular nuclei, while others were spindle shaped, with quite deep staining nuclei. The protoplasm was fairly abundant and moderately deeply stained. Where the muscle fibers were necrotic the proliferating cells were of the multinucleated, giant cell type. These muscle cells were hyaline-like to pale blue and some were fragmented. At times calcification was in progress in the necrotic muscle cells. In other places in this muscle, necrosis of muscle cells was the marked feature, with infiltration of leukocytes and the presence of cocci in the area. The lesions described above were noted in the gross as small spindle-shaped foci running in the long axis of the muscle fibers. On cross section they were observed as pinhead-sized, quite round, yellowish white dots scattered irregularly throughout the muscle. In one rabbit these areas were found in all of the skeletal muscles and the diaphragm. These observations resemble very closely those reported by Henrici.

Of the rabbits which showed exudative lesions in the muscles, two received *S. pyogenes hemolyticus* and one *S. infrequens*. Two other rabbits inoculated with *B. acidilactici* showed degenerative necrotic areas with marked hemorrhage. Fourteen animals showed interstitial hemorrhagic lesions. Six were inoculated with green streptococci, including *S. salivarius*, 5, and *S. equinus*, 1. Four received pure cultures of hemolytic streptococci, including *S. anginosus*, 1, *S. pyogenes*, 2, and *S. hemolyticus infrequens*, 1. One rabbit was given a mixture of *S. pyogenes* and *S. salivarius*, and another *S. pyogenes* and *Pneumococcus*. The last two rabbits were treated with *B. acidilactici*.

Kidneys—Several types of nephritis have been produced experimentally in animals by the employment of streptococci. Klotz³⁸ used the various members of the *S. viridans* group and found lesions in the kidneys similar to those reported by Gaskell³⁹ and Baehr⁴⁰ in man. This author also declared that the associated inflammatory processes of perivascular arrangement found in the heart, liver, joint capsules and other tissues suggest a common mode of attack by these streptococci on many tissues. Lecount and Jackson⁴¹ and Henrici²⁰ have described similar lesions in animals injected with different varieties of streptococci. The latter author found that the lesions were produced somewhat more frequently by hemolytic strains than by *S. viridans*, however, there was not observed any greater tendency of the former group to produce milary abscesses.

Of the rabbits among our animals which showed kidney lesions, six were injected with *S. salivarius*, one with *S. equinus* and four with hemolytic streptococci, including *S. pyogenes*, 3, and *S. anginosus*, 1. These lesions were observed in the gross on several occasions as small yellowish white dots scattered through the cortex. Two of these animals showed vegetative endocarditis as well as kidney changes. One was injected with *S. pyogenes* and the other with *S. salivarius*. Seven rabbits had myocardial changes as well as kidney lesions. Four of these animals received doses of *S. salivarius*, two *S. pyogenes*, and the last *S. anginosus*.

Several grades of reaction were noted. A number of animals included in the foregoing group of eleven showed varying degrees of hemorrhage into the glomeruli, tubules and interstitial tissues. The cells of the glomerular tufts were very much swollen, so that the space was obliterated at times, while again the injury was so great that hemorrhage took place into the capsular space. Where there was

38 Klotz. Canad. Pract. and Rev., 1914.

39 Gaskell. Jour. Path. and Bacteriol., 1912, **16**, 283.

40 Baehr. Jour. Exper. Med., 1912, **14**, 330.

41 Lecount and Jackson. Jour. Infect. Dis., 1914, **15**, 389.

hemorrhage into the tubules, the lining cells were in some cases hyaline in character, with indistinct nuclei. The inflammatory reactions consisted either of interstitial perivascular infiltration of lymphocytes and a few plasma cells, or, as in one case, of the formation of minute abscesses in the intermediate zone. At times the cells of the perivascular spaces were swollen and proliferating. Still another type of reaction showed plugs of cocci in the glomeruli. The confines of the Bowman's capsules were still visible, with the cells of the tufts pressed against the wall of the capsule, showing several layers where the outlines of the cells were indistinct. About the embolus of the cocci, and also among the remains of the tufts, there were swollen, proliferating endothelial cells. Some of these large mononuclear cells contained phagocytosed cocci. The nuclei of these cells were deeply staining and the protoplasm abundant. Lymphocytes and occasional leukocytes were observed in these areas. These lesions occurred following the injection of *S. viridans*. Concerning the other inflammatory changes described, no difference was noted in the relation of hemolytic and nonhemolytic streptococci to them.

Thymus—This organ quite frequently showed petechial hemorrhages throughout its structure. These lesions were scattered widely in the swollen glandlike structure in the form of bright red spots varying in size from that of a pinhead to small blotchy patches.

Sections of the thymus showed varying degrees of hemorrhage into the lobules of the lymphoid tissue. The tiny capillaries were engorged and distended with red blood cells and they had often ruptured, allowing the blood to spread widely into the tissue. There was no inflammatory reaction associated with the hemorrhage. In some places large endothelial cells were lodged in the lymph spaces with, at times, a moderate proliferation of these cells. The structure of the gland was mostly swollen and edematous.

Liver—Examination of the liver of these animals showed the presence of an exudative lesion twenty-nine times. Ten of these cases had been treated with hemolytic streptococci, including *S. subacidus*, 5, *S. pyogenes*, 3, *S. anginosus*, 1, and *S. infrequens*, 1. Of the remaining nineteen, sixteen had received strains of *S. viridans*, among which were *S. salivarius*, 11, *S. mitis*, 2, *S. fecalis*, 2, and *S. equinus*, 1. Two rabbits were injected with cultures of staphylococcus and one with *B. acidilactici*.

Microscopically, the reaction in the liver was observed in its initial stages as an accumulation of leukocytes within the sinusoids. These structures became distended and fibrin threads could be made out lying among the inflammatory cells. This reaction continued until the bordering liver cells were attacked when by extension a fairly well

defined area of necrosis was formed. The alteration occurred in any part of the lobule. At times the areas were quite small and scattered diffusely here and there. They were filled with leukocytes, degenerating liver cells and nuclear debris. Occasionally entire lobules were involved, with the dilated sinusoids packed with leukocytes and the broken liver columns were stained a homogeneous pinkish red. In several cases definite infarction occurred within the liver directly under the capsule where there was marked infiltration of leukocytes with the formation of small abscesses. Some livers showed an infiltration of lymphocytes in the portal system, while again areas of necrosis frequently bordered closely on these structures. However, the necrosis as a rule began with a crowding of the sinusoids by leukocytes and the reaction then advanced to destruction of liver tissue. In many sections the sinusoids were engorged with blood.

The reactions were noted with both hemolytic and nonhemolytic streptococci, although more frequently with the latter group. However, the reactions with the hemolytic streptococci were at times more intense.

Klotz and Bothwell⁴² have called attention to the necrosis found in rabbits treated with streptococci and lesions observed in our animals closely resemble their descriptions.

Lungs—Seventy-five of the animals showed very congested lungs, many of which presented definite circumscribed hemorrhages scattered over the pleura and throughout the tissue.

Sections of the lungs showed chiefly hemorrhage which was characterized by leakage of blood into the alveoli. This reaction was quite extensive in some places, while again it consisted more of blotchy patches lying close under the pleura. Very often the alveoli were distended with granular, pink-staining lymph either lying free or mixed with desquamated cells. At times the interalveolar capillaries were crowded with leukocytes and even formed small foci with evidence of necrosis. In several sections there was a marked infiltration of leukocytes into the intima of small arteries without involvement of the media. A free media separated the intima from the adventitia, which showed a similar reaction. Some vessels were plugged by thrombi, with invasion of the wall by leukocytes and extension into the surrounding tissue. Several times infarcted-like areas were encountered with the bordering reaction consisting of an admixture of leukocytes, lymphocytes and large endothelial cells.

The reactions observed in the arteries in the lungs are similar to those which have been described by me in the arteries of acute meningitis.

42 Klotz and Bothwell. Proc. Soc. Exper. Biol. and Med., 1914, **11**, 118.

GENERAL DISCUSSION

From the studies of a number of authors working with different organisms we have learned that the lungs, liver and spleen assume an important rôle in combating all types of infection. It would appear that all animals to a certain degree possess defensive properties against invasion of their blood stream and tissues by infecting agents. This property seems also to be regulated by several factors which influence the course of an infection and the ultimate fate of the host. The virulence of the organisms used, the dosage and the variations in the natural resistance of animals apparently in identical physical condition all contribute to irregularities in the course of experimental infections. We have pointed out elsewhere⁴³ the marked variations in the character of the infections produced in animals treated with the same organisms under identical experimental conditions. There can be but little doubt that natural immunity varies among animals the same as among human beings. With this fact in view the preciseness of interpretation of experimental bacterial infections must necessarily be limited. Particularly from the work of Bull⁴⁴ we have learned that the body is able to care for infection of a certain grade beyond which, however, the animal usually succumbs. This author has found that with the injection into rabbits of a quantity of virulent organisms sufficient to cause death within two to four days the septicemia takes a definite course with slight variations. The bacteria rapidly decrease in number from the time of injection for two to four hours, at which time the blood is sterile or contains only a few bacteria. Within five or six hours the bacteria reappear in the blood and steadily increase until the death of the animal. The initial disappearance of the organisms from the blood is due to the activity of the lungs and liver particularly, and in these locations the organisms are phagocyted following primary agglutination in the blood stream. We have noted in our experiments that these organs do not go unscathed in their effort to rid the blood of the invading organisms, as they quite frequently present areas of necrosis in their structures. Following this protective period the organisms multiply in the blood and vigorously attack the less resistant tissues where they grow and produce focal lesions. In our experiments very large doses of organisms were administered, with the result that the natural barriers of the body were overcome and a wide dissemination of organisms occurred. This widespread infection was attended by the development of focal lesions in many tissues without evidence of selective localization. Even where the

⁴³ McMeans *Am Jour Med Sc*, 1916, **151**, 249, *idem*, *THE ARCHIVES INT MED*, 1917, **19**, 709

⁴⁴ Bull *Jour Exper Med*, 1914, **20**, 237

same organism was used through several generations and over an extended period of time in rabbits there was little tendency for it regularly to attack a certain tissue. This phase of infection is particularly well illustrated in our work on experimental appendicitis where certain strains of streptococci were studied to determine selective qualities. From this we learned that organisms isolated from joints presented no tendency to localize exclusively in the joints of other intravenously treated animals. The same may be said of organisms isolated from other organs in respect to their source when injected intravenously into rabbits. From this it is difficult to conceive that different strains of the same organism should possess distinct localizing power and should vary consistently in their selective action. Further, the knowledge that we have gained of the mode of blood stream infection does not harmonize with the theory that organs exercise a peculiar avidity for particular organisms. The fate of living bacteria after their introduction into the blood stream of normal animals has been fairly definitely determined. Such organs as the lungs, liver and spleen act in the early stages as the protective barriers of the body. Depending on the dosage and virulence of the organisms used, these barriers may be overcome, and it is then that the less resistant tissues of the body are attacked. We cannot support the opinion that organisms possess a selective quality for organs, which is of a transient nature and disappears after a few days of artificial cultivation. In our work entitled "Experimental Appendicitis" we studied certain strains of streptococci over a period of several weeks and found that these organisms still would attack the appendix in one case after cultivation on blood agar for thirty-eight days with but one animal passage supervening. Another interesting feature which was noted consisted in the marked variation with which the different organs were attacked, even in animals injected with doses from the same subculture, no definite order of invasion was followed. Therefore, organisms which produce an appreciable percentage of lesions in organs other than those from which they are isolated cannot be listed as a particular organ strain.

Regarding the frequency with which the two types of streptococci attacked the several tissues, it was found that there were no marked differences in the percentages of lesions caused by hemolytic and non-hemolytic streptococci in the endocardium, skeletal muscle and periarthicular tissues. The green streptococci, however, more frequently produced vegetative endocarditis, while the hemolytic organisms were more commonly associated with subendocardial hemorrhages. In regard to the skeletal muscles, the hemolytic streptococci produced exudative lesions while the green streptococci were found only in connection with

hemorrhages Lesions in the heart and kidney were more frequently caused by green streptococci, although no great differences were noted between the character of this lesion and that produced by hemolytic streptococci In the third group of animals the percentage of lesions was in most cases high, due chiefly to the activity of the capsulated gram-negative bacilli A comparison of the percentages in the three groups of animals presents evidence that there was a general invasion of all the tissues in these animals There is no evidence to support the theory of selective localization beyond the view that the tissue forms a favorable nidus for the growth of an organism, due either to a peculiar susceptibility on its part or to injury during the "protective period" which precedes a general infection

Author's Note This work was carried out under the direction of Dr John A Hartwell, to whom I am much indebted for advice and assistance

PRIMARY ATROPHY OF THE PALLIDAL SYSTEM OF THE CORPUS STRIATUM

A CONTRIBUTION TO THE NATURE AND PATHOLOGY OF
PARALYSIS AGITANS¹

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INTRODUCTION

The nature of paralysis agitans has been an attractive subject for investigation ever since the publication of Parkinson's¹ celebrated "Essay on the Shaking Palsy" a century ago

Many strange theories have been advanced and innumerable lesions suggested in explanation of the peculiar phenomena of this interesting disease. But as our knowledge of the pathology and physiology of the nervous system has advanced, many hypotheses, at one time popular, have been discarded and now have only an historical interest. That the subject, however, is still shrouded in uncertainty and mystery, may be readily determined by a perusal of the more recent descriptions in authoritative textbooks of medicine and neurology.

In former years paralysis agitans was described by some authors with the functional diseases, while others believed it to be an affection of the muscular system. It has been held more recently to be related to certain of the ductless glands and especial reference has been made to the parathyroid glands. Many regions of the central nervous system have also had their special vogue and were believed to be the seat of the essential lesion, and it is not so very long ago that pigmentary degeneration of the large motor cells of the spinal cord or of the cerebral cortex was regarded with considerable suspicion in relation to the etiology of the disease.

Much emphasis has also been placed on the evidences of senile and vascular degenerations in the central nervous system of those suffering from this affection and a favorite pathologic theory was the perivascular sclerosis and perivascular gliosis — a not infrequent finding in the white matter of the spinal cord of the older cases — a pathologic condition, however, which is by no means limited to Parkinson's disease.

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¹ Parkinson, James. An Essay on the Shaking Palsy, London, 1817

PATHOLOGIC CHANGES IN THE BASAL GANGLIA

In recent years, pathologic interest has been chiefly centered in the large basal ganglia, namely, the corpus striatum and the optic thalamus—more especially since the publication of Jelgersma's² brief report of the pathologic findings in this disease. Jelgersma noted in a case of paralysis agitans distinct evidences of atrophy in the medullary radiations of the nucleus lentiformis, a reduction in the size of the ansa system—the ansa lenticularis and the ansa peduncularis, together with evidences of atrophy in Forel's field H_1 and H_2 , as well as atrophic changes in the nucleus lateralis thalami, the corpus Luysii and the medullary radiations of the substantia reticularis. He emphasized the fact that these atrophic changes in the corpus striatum, the optic thalamus and the hypothalamic region were quite evident and unmistakable.

Jelgersma's pathologic studies were reported only in abstract form, and while very brief and incomplete, they served to direct attention to this region and blazed the trail for much subsequent pathologic investigation.

In the chapter on the "Pathology of Paralysis Agitans," contributed to Lewandowsky's Handbook of Neurology, Lewy³ in a discussion of these findings, asserts that he has studied serial sections of five cases of paralysis agitans and that an essential atrophy of the ansa lenticularis and of the lenticular radiations does not occur. He modifies this opinion, however, by the statement that some diminution in the number of fibers in the ansa system is of frequent occurrence, and that this is especially well marked in those cases in which there are conspicuous vascular changes in the globus pallidus. In addition, he also notes the existence of atrophic changes in the nucleus basalis of Meynert, the nucleus lateralis of the thalamus and the nucleus paraventricularis thalami.

In a later contribution to the pathologic anatomy of paralysis agitans, Lewy⁴ states on the basis of a very extensive histopathologic study of the disease that the essential lesions are localized in the lenticular nucleus, the nucleus of the ansa peduncularis, and the sympathetic vagus nucleus of the medulla, that in typical cases there is a marked increase of the glia elements with degeneration of the ganglion cells, especially of the putamen, less of the globus pallidus, and that many of the ganglion cells show distinct senile fibrillary changes. He

² Jelgersma. *Neu Anat Befunde bei Paralysis Agitans und bei chronischen Chorea*, Neurol Centralbl, 1908, **27**, 995.

³ Lewy, F. H. *Paralysis Agitans*, Lewandowsky's Handbuch d. Neurol, 1912, **2**, 920.

⁴ Lewy, F. H. *Zur Path Anat der Paralysis Agitans*, Neurol Centralbl, 1913, **32**, 1305.

closes with the statement that these pathologic changes are essentially senile in character and is at loss to explain the occurrence of the juvenile types of the disease

Manschot,⁵ in an investigation of paralysis agitans, also found a diminution in the number of the ganglion cells and fibers of the optic thalamus, especially of the nucleus lateralis, as well as atrophic changes in the putamen of the lenticular nucleus and in the regio subthalamica

Quite recently, Auer and McGouch⁶ have reported the pathologic findings in two cases of paralysis agitans. In both cases the corpus striatum contained numerous small areas of rarefaction, giving the tissue a somewhat moth-eaten appearance. Many of these spaces contained blood vessels and were quite evidently enlarged perivascular spaces. This *état criblé* was most marked in the lenticular nucleus, but was also present in the optic thalamus, the caudate nucleus, the internal and external capsule and in the corpus subthalamicum of Luys. These observers also noted a reduction of the external medullary layer and the radial fibers of the globus pallidus and in one of the cases there was marked degeneration of cells of the centrum medium of the thalamus and the corpus subthalamicum. They state that the cells of the corpus striatum did not stain well, which may have been due to the age of the material.

It is, therefore, very apparent from this brief review of the more recent literature that certain definite pathologic alterations in the basal ganglia are fairly constant, that vascular and atrophic changes are demonstrable in both the optic thalamus and the corpus striatum, and that no definite concrete conception as to the nature or pathology of the disease has as yet been offered.

ANATOMIC CONSIDERATIONS

The corpus striatum in man is divided by the passage of the internal capsule into two structures, the *caudate* nucleus and the *lenticular* nucleus. The nucleus lentiformis is still further subdivided into an external segment, the *putamen*, and an internal segment, which is termed the *globus pallidus*. These anatomic divisions are purely topographical and are based on the gross appearance of the cells and fiber systems which constitute the ganglion.

Histologically, the putamen is identical in structure with the caudate nucleus, and these two structures constitute the *neostriatum* of comparative anatomy. Both have the same origin and histologic

⁵ Manschot. Paralysis Agitans, Amsterdam, 1904, F. van Rossen.

⁶ Auer and McGouch. Pathological Findings in Two Cases of Paralysis Agitans, Jour. Nerv. and Ment. Dis., 1916, **43**, 532.

characteristics, the caudate nucleus being simply split off from the putamen by the passage of capsular fibers

The globus pallidus is older phylogenetically than the caudate nucleus and putamen (*neostriatum*) and is for this reason sometimes termed the *paleostriatum*. It consists of two segments, an external and an internal, the segmental appearance being produced by the massing of nerve fibers in the lateral and mesial medullary laminae



Fig 1—Showing normal cell types of the caudate nucleus and putamen (*neostriatum*) Nissl stain A, large motor cell of globus pallidus type (pallidal cells), B, small ganglion cells of the *neostriatum* (*neostriatal* cells)

CELL TYPES OF THE CORPUS STRIATUM

From the standpoint of pathologic physiology, a much greater importance is to be attached to the various cellular types of this region than to the mere gross anatomic appearance and subdivisions (Fig 1)

The *neostriatum*, that is, the caudate nucleus and putamen, is composed of two separate and distinct types of cells, a *small cell type* and

a *large cell type* The smaller type of ganglion cell is of pyramidal or polygonal form, and give to the neostriatum a characteristic histologic picture Scattered among these smaller cells which are very numerous, are ganglion cells of much larger size, of multipolar form, containing a large nucleus, Nissl granules, and quite frequently a deposit of yellow pigment These *giant cells* of the neostriatum are histologically of the motor type and may be regarded as the homologues in the corpus striatum of the cells of Betz in the rolandic area of the motor cortex

The globus pallidus (paleostriatum) contains aggregations of ganglion cells which are also of the motor type These cells are of



Fig 2—The caudate nucleus (hematoxylin-eosin) Juvenile paralysis agitans of twenty-five years' duration Note atrophy of the large motor cells (A) of globus pallidus type (pallidal cells) The small ganglion cells are well preserved, there is moderate increase of glia cells

pyramidal and multipolar form, contain a large vesicular nucleus, Nissl granules and frequently clumps of yellow pigment They are of the same cellular type as are the giant motor cells of the neostriatum and I believe possess a similar function The corpus striatum is therefore composed of two distinct cellular types, namely, those of the large cell or motor type which is present in both the globus pallidus (paleostriatum) and the caudate nucleus and putamen (neostriatum), and a small cell type which is present only in the neostriatum

The large motor cells of *globus pallidus type* possess long axis cylinder processes and belong to Type I of Golgi's classification These

fibers course in the ansa lenticularis and ansa peduncularis terminating in the optic thalamus and hypothalamic region. This motor system I would term the *efferent pallidal system* of the corpus striatum, and the seat of the essential lesion in paralysis agitans.

The small cells of the neostriatum, on the other hand, have short axis cylinders and belong to Type II of Golgi's classification. They terminate in the external and internal segments of the globus pallidus. This is apparently a short association system which unites the caudate nucleus and the putamen to the globus pallidus. It is according to my conception merely an inhibitory and association system for the corpus striatum. This short *neostriatal system* undergoes atrophy in Huntington's chorea and is the essential lesion underlying the choreiform manifestation of this disease (Hunt⁷).

Two fundamental forms of motor disturbances are therefore referable to the cellular systems of the corpus striatum. Atrophy of the small cell or *neostriatal system* is followed by chorea of the Huntington type, while atrophy of the large cell or *efferent pallidal system* gives rise to the characteristic symptomatology of paralysis agitans.

PRIMARY ATROPHY OF THE PALLIDAL SYSTEM

In a previous monograph,⁷ I have considered at some length the functions of the corpus striatum in a discussion of the pathology of juvenile paralysis agitans and its relation to the *efferent pallidal system* of the corpus striatum.

In the case which formed the basis of this study the disease made its appearance in the fifteenth year, death supervening at the age of 40. The duration of the affection was therefore twenty-five years. Examination of the central nervous system revealed evidences of chronic cellular atrophy with considerable diminution in number of the large motor cells of the corpus striatum. The cellular atrophy was strictly limited to a definite system of cells, namely, those of the motor or globus pallidus type, while the smaller ganglia cells of the corpus striatum were unaffected. I therefore regarded the juvenile paralysis agitans as a motor system disease, the lesion being limited to the *efferent projection system* of the corpus striatum (Fig 2).

In addition to the cellular changes there were also evidences of atrophy in the course of the strio-hypothalamic radiations—the ansa system showing definite evidences of thinning. The theory was advanced that the corpus striatum contained an important motor system which was termed the *pallidal system*, which through its con-

⁷ Hunt, J Ramsay. Progressive Atrophy of the Globus Pallidus (Primary Atrophy of the Pallidal System). A Contribution to the Functions of the Corpus Striatum, Brain, 1917, 40, 58.

nection with important nuclei in the hypothalamic region, namely, the nucleus ruber, the corpus subthalamicum and the substantia nigra controlled and regulated the extra pyramidal motor system of the spinal cord, namely, the rubrospinal and other descending motor tracts

THE NATURE OF JUVENILE PARALYSIS AGITANS

The juvenile type of paralysis agitans was therefore regarded as a pure system disease, a neuronal *abiotrophy*, and the suggestion was made that it be distinguished from other types of the Parkinson syndrome as *primary atrophy of the pallidal system*. It was believed to be another evidence of the vulnerability of motor neurons, corresponding in this domain to primary lateral sclerosis and progressive muscular atrophy, as encountered in corticospinal motor neurons

The opinion was also expressed that Parkinson's disease is not a disease *suu generis*, but a syndrome, and that a variety of pathologic conditions may underly the symptomatology, for example, a primary atrophy or system disease, senile atrophy, vascular and inflammatory lesions, syphilis, tumors, etc

Evidence was also presented for regarding the corpus striatum and the striospinal system as a mechanism for the control and regulation of automatic and associated movements in contradistinction to the corticospinal system which controls and regulates the higher cortical motor activities, that is, isolated and dissociated movements

Paralysis agitans was therefore regarded as one of the fundamental types of central palsy characterized by paralysis of automatic and associated movements, rigidity and tremor. It was held that there are two types of central palsy, a *spastic paralysis* characterized by paralysis of isolated and discriminative movements, associated with spasticity of the musculature and referable to lesions of the pyramidal system, and a *paralysis agitans*, distinguished by a paralysis of automatic and associated movements, rigidity and tremor, and referable to lesions of the pallidal system

In the present study this question receives further consideration and confirmation. In two cases of paralysis agitans of the presenile type characteristic atrophic changes were demonstrable in the large motor cells of the corpus striatum and in the strio-hypothalamic radiations (ansa lenticularis and ansa peduncularis) which I have termed the efferent pallidal system of the corpus striatum

REPORT OF CASES

CASE 1—*Summary*—A man, aged 56, had presented typical symptoms of paralysis agitans for seven years prior to his death. There was general weakness and rigidity, rhythmical tremors of the extremities, face and tongue, the parkinsonian mask and the posture, attitude and gait typical of the disease. Death ensued from infection of the genito-urinary tract and lobular pneumonia

Histologic Study The central nervous system showed atrophic changes in the large motor cells of the neostriatum (giant cells of the caudate nucleus and putamen) with slight reduction of the medullary network of the globus pallidus and thinning of the strio-hypothalamic radiation—the ansa system of the corpus striatum

Clinical Diagnosis Paralysis agitans

Pathologic Diagnosis Primary atrophy of the pallidal system of the corpus striatum

History—The patient, aged 53, was for many years a watchmaker For fifteen years prior to admission he had been employed in the custom house service He was admitted to the Montefiore Home and Hospital, Sept 30, 1911, and gave the following account of his illness

Family History—This was negative Both parents were said to have died of old age, the mother suffering in the later years of her life from diabetes and asthmatic seizures Five brothers were living and in good health

Personal History—He had measles and scarlet fever in childhood and typhoid fever in his twenty-seventh year Eight years ago he developed symptoms of pulmonary tuberculosis with fever, night sweats, cough, loss of weight and hemoptysis At the end of a year these symptoms abated and he had apparently regained his previous health and strength He had always been moderate in the use of alcohol and tobacco With the exception of a mild attack of gonorrhea at the age of 45 he had been free from venereal disease There was no history of injury He married at the age of 26, and his wife bore three healthy children She died six years after marriage during confinement Subsequently he remarried and had two healthy children There were no miscarriages in either marriage

Present Illness—Three years before admission he experienced a peculiar weakness and stiffness of the right hand which came on gradually and interfered with proper movements of the extremities This was soon followed by a rhythmical tremor of the hand and fingers Later a similar tremor made its appearance in the left hand with some tremor of the head Subsequently his legs became stiff and weak and the gait slow and difficult There was also a tendency for the walk to develop into a more rapid pace and he was obliged to stop suddenly to avoid pitching forward (propulsion) The condition progressed slowly and was followed two years later by a feeling of general stiffness and rigidity and a constant rhythmical tremor About this time the articulation also became affected and his speech was tremulous and indistinct

He complained of no general cerebral symptoms and has been free from headaches and vertigo His memory is good and sleep is undisturbed The course of the disease has been slowly and steadily progressive, without pain or parasthesias and consists essentially of weakness and tremor which affects the speech and the movements of the trunk, arms and legs, more especially on the right side He does not complain of heat sensations or excessive perspiration There is some drooling of saliva from the mouth at night Occasionally there is dysuria and at times a purulent discharge from the urethra

Physical Examination—This was made in October, 1911 The patient was well nourished and presented no skeletal deformities He stood stiffly with the head and back somewhat bent There was considerable stiffness in the movements of the trunk The face was expressionless and masklike The musculature was stiff and passive movements showed a waxlike rigidity, the contour of the muscles stood out quite clearly Nearly all movements were performed slowly and with difficulty The gait was slow and shuffling, the steps short with a tendency to slouch and drag the legs When told to walk rapidly the movements became accelerated and propulsion developed There were evidences of tremor in all four extremities The arms were more tremulous than the legs and the right side was more affected than the left The tremor was especially well-marked in the hands and fingers and in the

right hand the posture and the tremor suggested the typical pill rolling movement of paralysis agitans

The tremor was slow and rhythmical, about three oscillations to the second. The amplitude of the tremor was not very marked and it continued steadily during rest. It varied occasionally in intensity. Usually an active movement of the extremities caused some diminution or even cessation of the tremor. It therefore lacked the quality of an intention tremor. The tremor sometimes increased during action, but always diminished on fixation as when the index finger is applied to the tip of the nose. There was also a slight rhythmical tremor of the lips and tongue. The facial innervation was not so strong on the right side which coincides with the greater involvement of the right arm and leg. The tongue was protruded in the median line and was tremulous. There was some tendency to drooling of saliva. The speech was very slow and drawing. The ocular excursions were normal, and there was no tremor of the ocular muscles. The eyelids were slightly tremulous. The palatal innervation was normal and a laryngologic examination conducted by Dr. Wolf



Fig 3 (Case 1)—Presenile paralysis agitans. Vertical section through the anterior portion of the corpus striatum (Weigert-Pal stain). Note diminution of the fiber network of the globus pallidus proper, the internal capsule is well preserved.

Freudenthal, the consulting laryngologist, showed normal conditions, there was no tremor of the vocal cords. The tendon reflexes of the upper and lower extremities were present and moderately active. There was no ankle clonus and the plantar reflex was of the normal type (no Babinski sign). The pupils were equal and reacted promptly to light and accommodation. The sensations, both superficial and deep, were normal. The outlines of the heart were normal and there were no murmurs. The radial pulses were equal, regular and of good quality. The chest was well developed, symmetrical, with good expansion. Percussion showed some dullness over the left apex. The breath sounds were wheezing and increased over both apices. The prostate gland was hypertrophied and there was residual urine of about 10 ounces.

Note—The clinical picture presented was typical of paralysis agitans. The patient remained in the Montefiore Home up to the time of his death in May, 1915, his condition gradually growing worse. The Wassermann test of the blood was negative. In November, 1914, he developed dysuria with some

purulent discharge from the urethra April 1, 1915, a testicular tumor developed on the right side, which was firm and tender and about the size of a small egg Dr Hauswirth, who examined the patient at this time, found that the enlargement was confined to the epididymis The inguinal glands were enlarged on both sides, more so on the right Systolic blood pressure, 115, diastolic, 85 Later the patient was unable to pass urine and catheterization became necessary

April 24, 1915, the right side of the scrotum was incised and 2 ounces of pus evacuated The urine contained albumin, numerous pus and blood cells Examination of the blood showed a well marked leukocytosis During the six weeks prior to his death there was irregular fever which reached 106 F ten days before death

Report of Necropsy and Pathologic Findings—The necropsy was performed seventeen hours after death by Dr A B Lambert, pathologist to the Montefiore Home and Hospital (Necropsy notes made by Dr Lambert)

Body That of a man measuring 158 cm in length, nutrition fair, rigidity present, postmortem hypostasis over dependent parts, moderate edema of feet and legs, no skin lesions present, no body deformities In the skin of the scrotum on the right side there is a linear scar about 3 cm in length to which the testis beneath is adherent The right testis is considerably enlarged and hard—the left appears to be slightly so The pupils are moderately contracted The majority of the upper teeth, especially on the right side are absent, and the remainder poorly preserved The mucosa of the mouth and eyelids is pale

Abdomen There is no exudate in the peritoneal cavity, the peritoneum is everywhere smooth and glistening The mesenteric lymph nodes are in places slightly enlarged The liver projects about 2½ cm below the costal margin in the right mammary line, its lower border shows a tendency to be rounded The appendix is quite small, is twisted upward behind the cecum, and measures about 5 cm in length The diaphragm extends to the fourth rib on the right side and fifth rib on the left side

Thorax The thymus is replaced largely by fat, both pleural cavities are free from fluid, both lungs are free except in the region of their apices, where they are tightly bound by old adhesions The pericardial cavity contains a slight excess of clear fluid, the pericardial surface is smooth and shiny There is a slight excess of epicardial fat

Heart The heart weighs 350 gm, the right auricle contains only a post-mortem clot The epicardium is everywhere smooth and shiny, the tricuspid opening admits the tips of three fingers, and measures in circumference about 11½ cm The cusps are quite delicate The right ventricular wall measures 3 to 5 mm Over the apex the muscle is replaced in considerable part by fat The musculature is rather pale The pulmonary opening measures about 7 cm The cusps are quite delicate The left auricle is normal The mitral valve easily admits the tips of two fingers and measures about 11 cm in circumference, its cusps are not thickened, although near the area of attachment there are a few yellow opacities which are distinctly seen on the ventricular surface The left ventricle appears to be slightly dilated, its wall measures about 1 cm in thickness The musculature in places has a distinctly grayish yellow cast, and the fibers look a little coarse The aortic opening measures 8 cm in circumference, its cusps are practically normal, as is also the first portion of the aorta The coronary vessels are practically free from atheroma

Lungs The right lung weighs 600 gm The periphery is everywhere smooth and free from exudate, except the apex, where there are some old fibrous tags, and there are numerous depressed scarred areas, which on palpation are firm and nodular The greater part of the upper and middle lobe is air containing, and moderately collapsed The lower lobe is much more voluminous, and its lower and posterior parts, while crepitant, are somewhat "meaty" on palpation Section through the upper lobe shows in region of the depressed areas many irregular, pigmented fibrous areas, and in addi-

tion a number of small gray nodules—evidently tubercles. Section through the remainder of the upper lobe and the median lobe shows dry, relatively nonpigmented air-containing lung tissue. The lower lobe, however, presents on section a bright red color. Some fluid and considerable blood exudes from the cut surfaces. There are some areas indefinitely outlined somewhat darker than the rest which suggest pneumonic consolidation, but they are not sharply circumscribed. The left lung weighs 450 gm. Superficially it is similar to the right. There are the same old tuberculous lesions in the apex. The lower lobe posteriorly is likewise heavy, filled with blood and a few distinct patches of lobular pneumonia can be made out.

Liver The liver weighs 1,875 gm. Both lobes of the liver are decidedly enlarged. The lower surface is distinctly rounded, especially the left lobe. The surface is smooth. The color is finely mottled, just beneath the capsule in the upper part of the right lobe there is seen a grayish yellow nodule which on section measures about 2 mm in diameter, evidently a calcifying thrombus in superficial vein. On cut section the lobulation is fairly distinct, the lobes



Fig 4 (Case 1)—Vertical section through the middle of corpus striatum, showing thinning of the ansa lenticularis and diminution of fiber network of the external segment of the globus pallidus

are of uniform size with reddish centers and slightly paler periphery. The gallbladder is filled with bile, its wall is thin, it contains no stones.

Spleen The spleen weighs 220 gm. It contains two deep notches on its upper border, it is firm, its capsule is not thickened. On section the lymphoid tissue is abundant and rather prominent. The trabeculae are not thickened.

Kidneys The right kidney weighs 150 gm and is of about normal size, measuring about 11 by 6 by 2½ cm. On removing the capsule a smooth surface is disclosed in which the vessels are decidedly injected. On section the cortex is seen to measure about 7 mm. The glomeruli are easily visible, the markings are regular. In one of the pyramids a small grayish yellow focus is seen, about 2 mm in diameter—evidently an abscess. The pelvis is dilated, its mucosa is thickened, the vessels decidedly injected, and occasional hemorrhages are seen. The ureter cusp in its lower portion shows less marked evidence of inflammation. The left kidney weighs 200 gm and is much enlarged, its capsule is easily removed. The surface is of a deep red hue. On section a quantity of blood exudes from the cut surfaces, the cortex mea-

tures about 8 mm in thickness, the markings are normal. Occasional gray yellow foci are seen in the pyramids. The pelvis is somewhat dilated. The ureter is dilated, and its mucosa presents the same appearance as that of the pelvis of the kidney.

Bladder The tissues around the bladder are extremely edematous, the bladder itself is distended with very foul, purulent urine, its wall is greatly thickened, measuring 15 cm in most places. The crests of the mucosa are of a reddish black color, showing in places grayish exudate. In general, however, there appear to be no ulcerations. The vessels are all greatly injected. There are a number of small crypts and diverticula present in all parts of the bladder. Between the folds of the mucosa the inflammatory condition is less marked, the mucosa being edematous but not particularly injected, and showing no definite exudate.

Prostate The prostate is enormously enlarged, measuring roughly $3\frac{1}{2}$ cm anteroposterior diameter. The enlargement is uniform. No definite abscesses are seen, but from the seminal vessels a purulent fluid can be expressed. The right testis, except for some increase in consistence, appears normal. The right epididymis, however, is greatly indurated, and shows a number of purulent foci. The wall of the vas deferens is considerably thickened. The left testis and epididymis are similar to the right, though the changes in the epididymis are less marked.

The esophagus is normal. The stomach shows postmortem digestion. The intestines, pancreas, larynx, trachea and thyroid are normal.

Parathyroids These were removed for microscopic study.

Aorta Shows a few early atheromatous changes throughout its entire extent. The iliacs show a striking longitudinal wrinkling.

Brain The brain weighs 1,260 gm. The skull is normal, the meninges are normal, slight edema of the pia arachnoid. There is a marked arteriosclerosis of the basilar vessels of the circle of Willis. The brain and cord were placed in formalin and preserved for microscopic study.

Histologic Study of the Glands and Viscera—(Dr Lambert) **Heart** In places the muscle fibers are quite large. There are occasional small scars.

Lungs Section 1—There are patches of confluent lobular pneumonia. In the exudate there are many red blood vessels and much pink staining coagulated fluid. The bronchi are filled with pus. Section 2—This includes a large nodule made up of old pigmented scarred tissue in which a number of fresh tubercles are seen and occasional lymphoid nodules. The tubercles all show large giant cells, in at least one of the giant cells there is one of the curious star-shaped glassy structures such as have been described by Wolbach, Wood and others (Proc New York Path Soc., May, 1915).

Kidneys The parenchyma is practically normal. The pelvic fat is increased in amount. The submucosa of the pelvis is thickened and infiltrated with leukocytes, and contains nests of epithelium, probably representing new growths from the mucosa (cystitis cystica?). No exudate on the surface is seen.

Liver The cells around the efferent vein contain a considerable quantity of yellowish-brown pigment. There is a slight increase of connective tissue about the portal vessels.

Bladder There is a marked hypertrophied muscular element. The mucosa is much thickened. Its epithelial covering is gone, leaving a very vascular hemorrhagic ulcerated surface. There is a great infiltration of the mucosa by wandering cells of all types.

Ureter The wall seems thickened, but there is no evidence of an acute inflammatory reaction.

Seminal Vesicles The connective tissue and nuclear elements are greatly increased. There is a slight infiltration by wandering cells, especially eosinophils. There is a marked papillary growth from the mucosa of the ducts. The papillae and polypoid masses are composed of cellular connective tissue and are covered by cuboidal or flattened epithelium.

Vas Deferens The wall is enormously thickened, and shows chronic inflammatory changes

Prostate The parenchyma is rather abundant. Many of the follicles are dilated and contain a lot of necrotic epithelium and pink staining fibrinous material. Other glands show a papillary hyperplasia of the lining cells. There is very little in the way of inflammatory reaction.

Testis and Epididymis There is a great increase of connective tissue stroma of the epididymis. There is also a diffuse fibrosis of the testis, and the tubules are small and atrophic looking—resembling more those of the kidney than normal testis. The larger blood vessels show thickened walls.

Hypophysis The glandular portion is normal. The pars nervosa contains a number of pigment containing cells. The pigment is in the form of small uniform hyaline granules.

Skeletal Muscles (Biceps) The muscle fibers are small, and the sarco-nuclei increased in number. Occasional encysted trichinae are seen. The capsule is a pink staining, hyaline, laminating material. In the parasites fine particles of lime are deposited.



Fig 5 (Case 1)—Vertical section through the optic thalamus and corpus Luysii, showing thinning of the strio-hypothalamic radiations

Thymus The thymus is made up chiefly of connective tissue and fat separating islands of thymic tissue. In these islands there are occasional small cysts containing necrotic pink staining material.

The parathyroids revealed no pathologic changes.

Microscopic Examination of the Central Nervous System—Sections were made from the cerebral cortex, the cerebellum, pons, medulla oblongata and spinal cord. The basal ganglia were cut in serial section and stained with toluidin blue, hematoxylin-eosin and by the Weigert-Pal method.

Spinal Cord Sections of the cord show no essential changes. The anterior horn cells are well formed, presenting a normal tigroid appearance, a well formed nucleus and nucleolus and well developed processes. There are no pathologic alterations of the Nissl granules, and no excess of pigment. Rarely a somewhat shrunken cell is observed, but these are quite isolated and infrequent.

There is no thickening of the meninges and the blood vessels are free from thrombi or noteworthy arteriosclerotic changes. There is no perivascular sclerosis, or gliosis. There is a considerable deposit of corpora amylacea in the

region of the posterior columns and posterior horns Weigert-Pal sections show no evidences of tract degeneration There are no signs of sclerosis in the areas occupied by the direct and crossed pyramidal tracts

Medulla The nuclei and nerve tracts are normal in appearance, and show no signs of degeneration or atrophy

The pons varolii is also normal The fillet, pyramidal tracts, the posterior longitudinal fasciculus and peduncles are normal

Cerebellum Sections of the cerebellar cortex including the dentate nucleus are normal The cellular layers of the cerebellar cortex including the large cells of Purkinje are well preserved and of normal appearance

Cerebral Cortex Sections from the frontal, rolandic and occipital areas show no essential lesions The cellular layers and medullary radiations present a normal appearance and especially noteworthy is the preservation of the large pyramidal cells of the motor area The cells of Betz are preserved and show no evidences of atrophy Occasional atrophic cells are noted in the cortex, more especially in the frontal region, but these are isolated and comparatively infrequent The meninges are normal and the blood vessels show moderate thickening of their walls

The basal ganglia were sectioned in serial slices, some of these were cut in thin sections (10 microns) and stained by various cellular methods, the remainder were treated by the Weigert-Pal method This permitted a fairly complete survey of the various structures and levels of the corpus striatum and of the optic thalamus for both cellular changes and tract degeneration (The serial sections of the basal ganglia were prepared in the New York Psychiatric Institute under the direction of Dr Charles B Dunlap)

Caudate Nucleus and Putamen The large ganglion cells of the globus pallidus type (giant cells) which are scattered through the neostriatum show well marked atrophic changes in the head, body and tail of the caudate nucleus and the putamen They are apparently not reduced in number Generally speaking, these atrophic changes are more marked in the anterior portions of the striatum The giant cells are considerably shrunken and reduced in size, the nucleus is absent or displaced laterally, very much contracted, presenting a shrunken, shrivelled appearance The processes of the cells are often fragmented or atrophic and of cork-screw or twisted configuration Many of the cells contain an excess of coarse yellow pigment granules, and not infrequently the pericellular and perivascular spaces in this region are observed to contain detritus consisting of granules of a yellowish lipid material

The small ganglion cells of the caudate nucleus and putamen are normal in number and appearance and the evidences of cellular atrophy are therefore limited to the large motor cells of the globus pallidus type, namely, the giant cells of the neostriatum There is no distinct increase of glia elements, although the pericellular spaces of atrophic cells sometimes contain small groups of parasite glia nuclei

The atrophy of the ganglion cells in the caudate nucleus and putamen is therefore a selective one, limited to a single and definite cellular type, namely, those of so-called *globus pallidus type* These cells have the structure and appearance of motor cells and are not unlike those of the rolandic area of the cerebral cortex and the anterior horns of the spinal cord

Globus Pallidus The ganglion cells of the globus pallidus proper (paleostriatum) are not reduced in number and are not definitely atrophic, many however, appear reduced in size and present a rounded or somewhat angular appearance The nucleus and nucleolus are preserved but frequently appear smaller than normal, and the Nissl granules are often absent or not sharply defined, the protoplasm appearing homogeneous and of a somewhat hyaline appearance Many of these cells contain a considerable amount of yellow pigment

The blood vessels of the corpus striatum and especially of the globus pallidus show some arteriosclerotic changes with thickening of the vessel walls,

more particularly of the media. There are no thrombotic occlusions, and no areas of softening or hemorrhage are noted. Many of the perivascular spaces contained clumps of yellowish and dark granular pigment and in the globus pallidus these are somewhat dilated. The dilatation of the perivascular spaces in the more anterior portions of the globus pallidus producing a slightly cribriform appearance (*état criblé*).

The ganglion cells of the *corpus Luysii*, *nucleus ruber*, and the *substantia nigra* appear normal in the specimens examined, except for an occasional isolated atrophic cell.

The optic thalamus shows no evidences of cellular changes or atrophy except for an occasional atrophic cell which stands out sharply from the normal cell groups. The cells of the *nucleus internus*, *nucleus medialis*, *nucleus lateralis* and the *nucleus anterior* are normal in appearance and number.

The blood vessels of the thalamic region show arteriosclerotic changes with thickening of the vessel walls and occasionally a dilated perivascular space. There are, however, no evidences of thrombosis, hemorrhage or softening.

Basal Ganglia (Weigert-Pal method) [Figs 3, 4 and 5] The general topography and medullary markings of the corpus striatum are well-preserved. There are no evidences of gross vascular lesions. The small pencil-like medullary bundles of the caudate nucleus and putamen are normal in size and appearance, as they traverse the neostriatum and may be traced into the globus pallidus.

The medullary network of the globus pallidus proper appears to have undergone a slight fiber reduction so far as it is possible to judge by this method. The reduction in the medullary network is more apparent in the anterior portion of the globus pallidus and involves especially its external segment, the external medullary lamina and the supplementary external lamina. The internal medullary layer appears to have undergone only slight if any reduction in its fiber content. The ansa lenticularis in its more anterior portion also shows some thinning of its fiber content and this atrophy appears to be more evident on one side than on the other. More posteriorly the ansa peduncularis appears to have undergone only very slight atrophy, which is also true of Forel's lenticular bundle (H_2) and the striolusian fibers.

Forel's commissure and Meynert's commissure of the hypothalamic region are both present and have apparently suffered no reduction in their fiber content. Forel's thalamic field (H_1) is also normal and the medullary capsule of the red nucleus is apparently not reduced in size. The corpus Luysii shows no evident diminution of its fiber content and only slight if any reduction of its medullary capsule. The internal capsule and the pes pedunculi are normal. There are no evidences of atrophy in the pyramidal tracts of the crus cerebri or of the brachium conjunctivum. In the fasciculus longitudinalis posticus and the tegmental region there is no obvious loss of nerve fibers.

The external and internal medullary layers and the *zone grüllagée* of the optic thalamus are normal, and there is no evident reduction of the striothalamic radiations.

The only demonstrable pathologic changes were the atrophy of the large ganglion cells of the caudate nucleus and putamen (the neostriatum) and a corresponding diminution of the fiber network of the globus pallidus and of the striohypothalamic radiations.

CASE 2—*Summary*—A man, aged 52, presenting the typical clinical picture of paralysis agitans of ten years' duration. There was general rigidity and tremors of the paralysis agitans type, a parkinsonian mask, almost complete dysarthria, and the gait and attitude typical of this disease. Death from bronchopneumonia.

Histologic Examination. Central nervous system revealed atrophic changes in the large motor cells of the corpus striatum, namely, the caudate nucleus and putamen. Many of the giant cells of the neostriatum were in various stages of chronic cellular atrophy. In addition there was some loss of the

medullary network of the globus pallidus and a thinning of the striohypothalamic radiation, namely, the fibers of the ansa system

Clinical Diagnosis Presenile type of paralysis agitans

Pathologic Diagnosis Primary atrophy of the pallidal system of the corpus striatum

History—The patient, aged 52, was a manufacturer of dress trimmings. He was admitted to the Montefiore Home and Hospital Nov 4, 1914. Owing to the speech disturbance much of the history was obtained from his mother.

Family History—His father died of cancer, aged 67. His mother, aged 68, is in good health. There is no history of any familial disease. The patient is the oldest of six children and emigrated to this country twenty years ago. He married but was divorced and had no children. No history of venereal disease was obtained. He had been engaged for many years in the manufacture of dress trimmings and was moderate in the use of alcohol and tobacco.

Present Illness—The malady from which he now suffers made its appearance ten years before admission to the hospital and began with weakness of the arms and hands. He was soon forced to give up work and remained at home, the arms gradually growing weaker. Subsequently a rhythmical tremor developed which has continued ever since, gradually increasing in extent and severity. Later the legs became affected and for the past four years the gait has shown considerable impairment. There also developed a curious tendency to acceleration of the step in walking (propulsion) from which he suffers at the present time. For the past three years the speech has shown distinct impairment and there is now considerable difficulty in forming words. There is a constant tendency to drooling of saliva and some difficulty in deglutition. All movements are labored and difficult and with the tremor and marked dysarthria a state of considerable helplessness has resulted. During his long illness there has been no history of general cerebral symptoms such as headache, vertigo, or apoplectic attacks, and the whole progress of the disease has been slowly and insidiously progressive.

Physical Examination—The patient walks slowly and with great difficulty, owing to the general rigidity of the musculature. A well marked tendency to propulsion is present. The attitude and gait are typical of paralysis agitans. Both the arms and legs are rigid on passive movement and there is well marked rigidity of the abdominal musculature. The contour of the muscles is very well defined and the musculature presents a waxlike firmness on direct pressure. The tendon reflexes of the upper and lower extremities are present and are not exaggerated. The plantar reflexes are normal. The abdominal and cremasteric reflexes are present and equal on the two sides. The pupils are equal and react to light and accommodation. There is no nystagmus or tremor of the ocular muscles. Sensation is quite normal. The mentality so far as could be determined was not affected. The outlines of the heart are normal and there are no murmurs. The radial pulse is regular—84 beats to the minute and equal on the two sides. Systolic blood pressure, 120. The lungs are normal to percussion but auscultation is unsatisfactory owing to the poor expansion of the chest. So far as could be determined the breath sounds are normal. Urine acid, specific gravity, 1.030, no albumin and no sugar.

Note—The patient remained in the neurologic wards of the Montefiore Home in practically the same condition until April 9, 1915, when symptoms of pneumonia developed. His breathing became rapid and labored, temperature rose to 104.6 F, pulse 110. Dulness on percussion was noted over the right lower lobe, with bronchovesicular breathing anteriorly and diminished sounds posteriorly. April 11, 1915, his condition was much worse and he became stuporous, with stertorous breathing. Examination of the cerebrospinal fluid was negative. The Wassermann test was negative. Death occurred April 12, 1915.

Report of Necropsy and Pathologic Findings—(Necropsy notes made by Dr A B Lambert) Body That of a moderately emaciated man, 158 cm in length There is a distinct curvature of the back, with drooping forward of the shoulders There are no skin lesions

Abdomen There is no fluid The intestines are freely movable The appendix extends into the pelvis, and measures about 6 cm in length The mesenteric glands are not enlarged The liver projects about 3 cm below the costal margin The thymus is atrophic Both lungs are free anteriorly The right is densely adherent to the diaphragm about the base The pericardium contains about 30 cc of clear fluid

Heart It weighs 260 gm It is distended with blood, especially on the right side The pericardium is everywhere smooth The precordial auricle is normal The tricuspid opening admits three fingers, and measures in circumference about 11 cm There is a slight thickening, especially of one of the cusps The right ventricular wall measures about 4 mm in thickness The pulmonary valve is normal and measures about 7 mm in circumference The



Fig 6 (Case 2)—Presenile paralysis agitans Vertical section through anterior portion of corpus striatum (Weigert-Pal stain) Note diminution of the fiber network of the globus pallidus proper, the internal capsule is well preserved

left auricle is normal The cusps of the mitral valve are moderately thickened, especially near their margin, but no fresh vegetations are seen The left ventricular wall measures about 13 mm in thickness The aortic valve measures 8 cm in circumference—its cusps are practically normal The aorta is quite elastic, and shows only very early atheromatous changes

Lungs The right lung is very voluminous, and weighs 1,100 gm Anteriorly is air-containing, but posteriorly is firm and nodular The pleura presents a mottled black and gray color, from the enormous amount of coal pigment present On section through the firm consolidated portion there is seen a patchy consolidation, the consolidated parts being lighter in color and slightly elevated above the surface From the bronchi there exudes thick, creamy pus In the lower lobe there is an area to which the diaphragm is firmly attached, and which shows on section an irregular cavity about 2½ cm in length which connects with the small bronchus A necrotic, purulent but not very foul material fills this cavity The larger bronchi are filled with pus

The glands about the hilum are deeply pigmented, very firm and in some places suggest calcification

The left lung is similar to the right, weighs 800 gm. The glands at the hilum are quite firm, pigmented, and there is one which on section shows grayish yellow, suggesting tubercle

Liver Weighs 1,400 gm. It presents a normal shape, except for a perpendicular depression over the right lobe. At one point on the surface is seen a small number of yellow nodules which project slightly, and which on section are distinctly caseous. The nodules measure about 0.5 mm in diameter and extend for a similar distance into the lobe. On cut section the liver is grayish red in color—the lobulation is fairly distinct. The gallbladder is unusually long, and contains no stones.

Spleen Weighs 150 gm. Is normal in shape. It is quite firm on section. The trabeculae are prominent. In the capsulae are seen a number of tiny gray nodules, less than 1 mm each in diameter—they do not extend into the substance of the spleen. The malpighian bodies are not very distinct.

Kidneys These organs together weigh 300 gm and are alike. The capsules strip easily. The cortex measures from about 6 to 7 mm. The glomeruli are quite prominent. There is a fair amount of pelvic fat. The pelvis and ureters are not dilated.

Bladder and Prostate These are normal.

Pancreas and Stomach These show the usual postmortem changes.

Larynx, Trachea and Thyroid Normal.

Brain There is a definite edema of meninges of the upper convexity. The sulci are quite wide and deep, suggesting some atrophy, especially in the frontal portion of the cerebrum. Section through formalin hardened specimen shows no gross lesion. The cortex does not appear to be definitely reduced in thickness. The vessels of the circle of Willis show some arteriosclerotic plaques but no evidence of thrombosis. The cord presents normal architecture and appearance. The brain and spinal cord were preserved in formalin for histologic examination.

Microscopic Examination of the Glands and Viscera—(Made by Dr Lambert.) **Heart** The muscle fibers are rather small. They contain, however, very little pigment. There is a slight increase in connective tissue about the blood vessel.

Lung Section 1—There is a confluent lobular pneumonia in the lower areas, polynuclear leukocytes predominate in the exudate, about the borders of such areas the alveoli contain many large mononuclear cells and a considerable quantity of coagulated fluid. In some of the alveoli are bluish masses suggesting bacteria. The bronchi are filled with pus cells.

Section 2 (through the cavity near base of right lung)—There is on one side a necrotic surface, in this is seen a vascular granulation tissue which merges gradually into the adjacent lung tissue. The lung alveoli are all collapsed. There is a great increase in the thickness of the septa. The pleura is also greatly thickened. The fibrosis suggests a chronic lesion—probably a bronchiectatic cavity. This cavity may have served as the starting point of the extensive lobular pneumonia. The blood vessel walls are rather thick, the sinuses are filled with blood. The trabeculae are of normal size.

Liver The section includes one of the caseous foci observed beneath the capsule—the connective tissue capsule surrounding this caseous material is undoubtedly an old thrombus mass. There appears to be little tendency toward organization. The liver itself presents the picture of a moderate chronic passive congestion. The capillaries are dilated, but there is no necrosis of liver cells.

Kidneys The organs show no marked alteration.

Prostate The follicles are rather large and abundant.

Thyroid The follicles are not very large, but contain abundant colloid, which stains well.

Parathyroids There is some increase in connective tissue about the larger blood vessels. The cells appear normal.

Arm and Neck Muscles Appear normal.

Muscle of Back The muscle of back stains very poorly—changes seen are probably postmortem.

Histologic Examination of the Central Nervous System—The brain and spinal cord were preserved in formalin and studies were made of the cerebral cortex, the cerebellum, medulla oblongata, pons varoli, spinal cord, the corpus striatum, optic thalamus and subthalamic region. The following stains were used: Toluidin blue (Nissl), hematoxylin-eosin, Sim's stain, and the Weigert-Pal method. Serial sections from the region of the basal ganglions were prepared in the New York Psychiatric Institute under the direction of Dr. Charles B. Dunlap. The basal ganglions were cut in vertical slices some of which were stained for cellular studies and the remainder cut in serial sections and stained by the Weigert-Pal method.

Spinal Cord The anterior horn cells are normal in appearance and in number. The nucleus is large and well formed, the nucleolus stands out clearly.

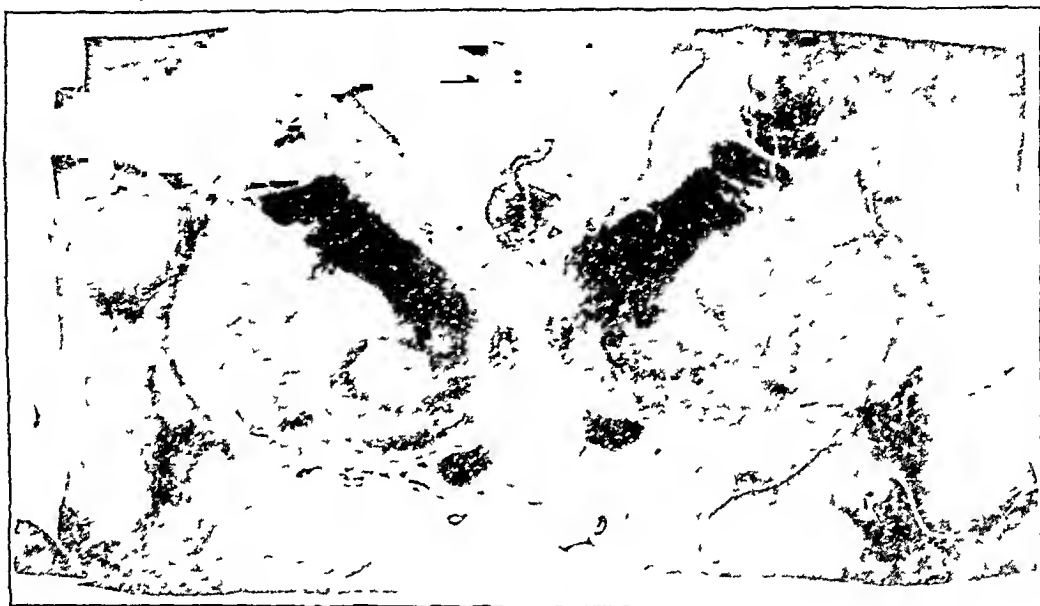


Fig 7 (Case 2)—Vertical section through middle of corpus striatum showing thinning of the ansa lenticularis and diminution of fiber network of the external segment of the globus pallidus.

and the normal tigroid appearance of the Nissl granules is well defined. There is no excess of pigment. The meninges and blood vessels show no noteworthy alteration. There is some thickening of the media in certain of the vessels, but no evidences of thrombosis or of hemorrhage. There are numerous corpora amylacea scattered throughout the section, especially in the region of the substantia gelatinosa of the posterior horns. There are no signs of perivascular gliosis or sclerosis. Weigert-Pal studies show no evidences of tract degeneration and the regions occupied by the direct and crossed pyramidal tracts show no sclerosis. Sections of the medulla oblongata are normal. The pyramids, the lemniscus and other tracts of the medulla are well formed and show no signs of atrophy. The nuclei of this region are normal. The pons varoli is normal.

Cerebral Cortex Sections were made of the frontal, occipital and rolandic areas. The cyto architecture was normal, and there was no extensive evidence of cellular atrophy or degeneration. Here and there atrophic ganglion cells, intensely stained, were noticeable, but such cells were few in number and widely

separated. The cells of Betz in the precentral convolution were well formed and free from atrophic changes. The medullary rays and markings of the cortex by Weigert's method were of fairly normal appearance and showed no especial diminution. The cerebellar cortex and dentate nuclei are normal. The cells of Purkinje are well formed and of normal appearance.

Optic Thalamus. Sections through the anterior, middle and posterior portions of the optic thalamus show no essential lesions. The cells of the nucleus anterior, nucleus lateralis and medialis are not diminished in number and show no evidences of atrophy. The medullary laminae of the thalamus are well preserved, as are Forel's thalamic bundle H_1 and the medullary capsule of the nucleus ruber. The cells of the corpus Luysii are well preserved and free from atrophic changes.

Corpus Striatum. The caudate and the lenticular nuclei are free from any evidences of gross lesions. The blood vessel walls are thickened, especially the middle coats, but the lumen is free and there are no thrombi. In the globus pallidus the perivascular spaces are rather large and there is a slight cribriform appearance as a result of these vascular and perivascular changes. Many of the perivascular spaces contain clumps of yellow and dark brown pigment (lipoid material) and such pigment granules are also encountered in some of the perivascular spaces.

Ganglion Cells of the Corpus Striatum. The small cells of the caudate nucleus and of the putamen are normal in number and appearance. In contrast to these, the large motor cells of the globus pallidus type in the caudate nucleus and putamen show definite signs of atrophy. These changes are especially well marked in the more anterior portion of the ganglia. The atrophic changes in the large multipolar cells of the neostriatum (giant cells) consist of shrinkage and atrophy of the cell body, thin and atrophic processes, a small, irregular and displaced nucleus staining a uniform and intense blue with hematoxylin. In some cells the atrophy and shrinkage are so marked as to prevent the differentiation of nuclear structure. Such cells are often shrunken and of a hyaline appearance. In many of the cells the protoplasm is broken up into coarse granules of a yellowish tinge and appear to have undergone pigmentary degeneration. Many of the atrophic cells are surrounded by groups of parasite glia cells, lying in the pericellular spaces. These changes, which are quite general and well marked in the more anterior portions of the corpus striatum, are less prominent more posteriorly.

Globus Pallidus. The large multipolar cells of the globus pallidus type are well preserved and are not diminished in number. Many of these cells, however, are somewhat reduced in size and present a more rounded or angular appearance than usual. Many of the cells are filled with coarse, light yellow pigment granules. The nucleus and nucleolus are well preserved. The fiber systems of the corpus striatum by the Weigert-Pal method show slight but distinct evidences of atrophic changes. The small pencil-like medullary bundles which pass from the caudate nucleus and the putamen into the globus pallidus are well preserved and have undergone no reduction in size or number. The external medullary lamina and the supplementary external lamina of the globus pallidus appear distinctly thinner than normal, and the external segment of the globus pallidus shows a distinct reduction in its network of medullated nerve fibers (Figs 6, 7 and 8). In the anterior portions of the globus pallidus the diminution of the fiber network is quite marked. The ansa lenticularis and ansa peduncularis are fairly well preserved but especially in the more forward portion of the ansa system appear thinned and atrophic. A slight thinning of Forel's field H_2 and of the strio-luysian fibers is also present. Meynert's commissure and Forel's commissure are present and apparently have undergone no diminution in size. The essential pathologic changes were an atrophy of the large ganglion cells of the caudate nucleus and putamen (neostriatum) and a corresponding diminution of the fiber network of the globus pallidus and of the strio-hypothalamic radiations or ansa system.

COMMENTS ON THE PATHOLOGIC STUDIES OF CASES 1 AND 2

The cases just recorded are typical examples of the presenile type of paralysis agitans. In Case 1 the duration of the disease was about seven years and in Case 2 approximately ten years, both died of acute intercurrent affections. All of the cardinal symptoms of the disease, namely, paralysis, rigidity and tremor were present and quite generalized.

In the examination of the central nervous system, especial attention was given to the basal ganglia. In these structures there were no evidences of gross lesions, such as hemorrhage, softening or inflammation. The blood vessels were somewhat thickened, especially in the



Fig 8 (Case 2)—Vertical section through the optic thalamus and corpus Luysii, showing thinning of the strio-hypothalamic radiations

region of the globus pallidus, where a slight appearance of *état criblé* was produced. There were, however, no evidences of thrombosis.

The most striking pathologic changes noted were in the large motor cells of the caudate nucleus and putamen. Many of these giant pallidal cells of the neostriatum were in various stages of chronic cellular atrophy (Fig 9). The cells were reduced in size, the bodies shrunken, atrophic and shivelled processes, with an elongated contracted nucleus, occupying a lateral position in the cell body. Pyknosis of the nucleus was a very striking feature in many cells, while in others the entire cell was much shrunken and diffusely stained. Many cells showed evidences of advanced pigmentary degeneration and many of the perivascular and pericellular spaces of the corpus striatum contained pig-

ment detritus and yellowish lipid material. The large cells of the striatum did not appear to be reduced in number, but were simply in various stages of chronic atrophy; there was no noteworthy increase of the glia cells in this region.

In contrast to the atrophic changes in the giant pallidal cells of the neostriatum, the small ganglion cells of this region (neostriatal cells) were preserved, both in number and appearance, and were free from evidences of atrophy (Fig 9). The cellular changes were more pro-

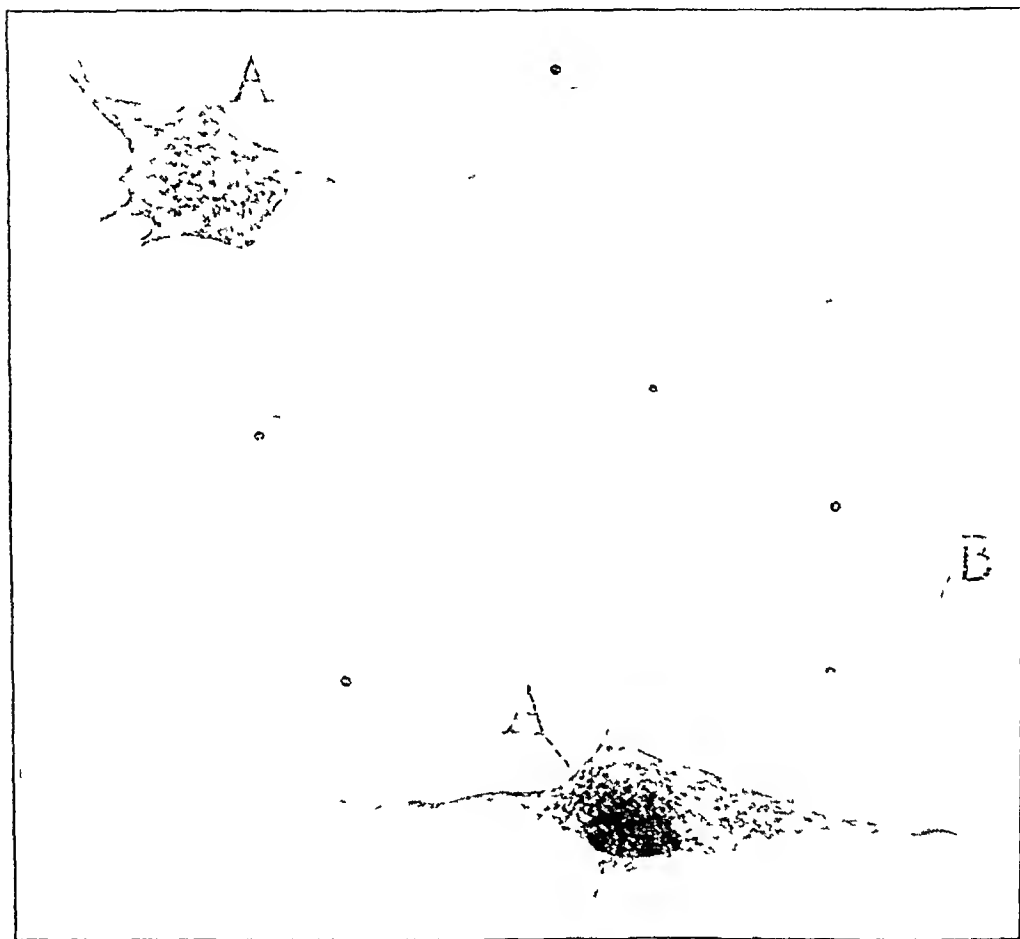


Fig 9—Showing atrophic ganglion cells of the caudate nucleus and putamen (neostriatum). Nissl stain. Presenile paralysis agitans of ten years' duration. *A*, atrophy of large motor cells of the pallidal type; *B*, small ganglion cells are normal.

nounced in the anterior portion of the corpus striatum, although occasional atrophic cells of the large globus pallidus type were demonstrable as far posteriorly as the tail of the caudate nucleus.

The motor cells of the globus pallidus proper (the paleostriatum) were not reduced in number, and in comparison with the giant pallidal cells of the neostriatum were well preserved. Many of these cells gave the impression, however, of being somewhat reduced in size and

of presenting a more rounded and angular appearance than do normal cells. Their internal structure, including the nucleus and nucleolus was well preserved.

In serial sections, stained by the Weigert-Pall method, certain pathologic changes were also apparent in the corpus striatum (Figs 3, 4, 5, 6, 7 and 8). The medullary network of the globus pallidus, especially in its anterior portion, had suffered some reduction in the number of its nerve fibers and the external segment had apparently suffered more in this respect than had its internal segment. The reduction was present in both the external medullary and the supplementary external

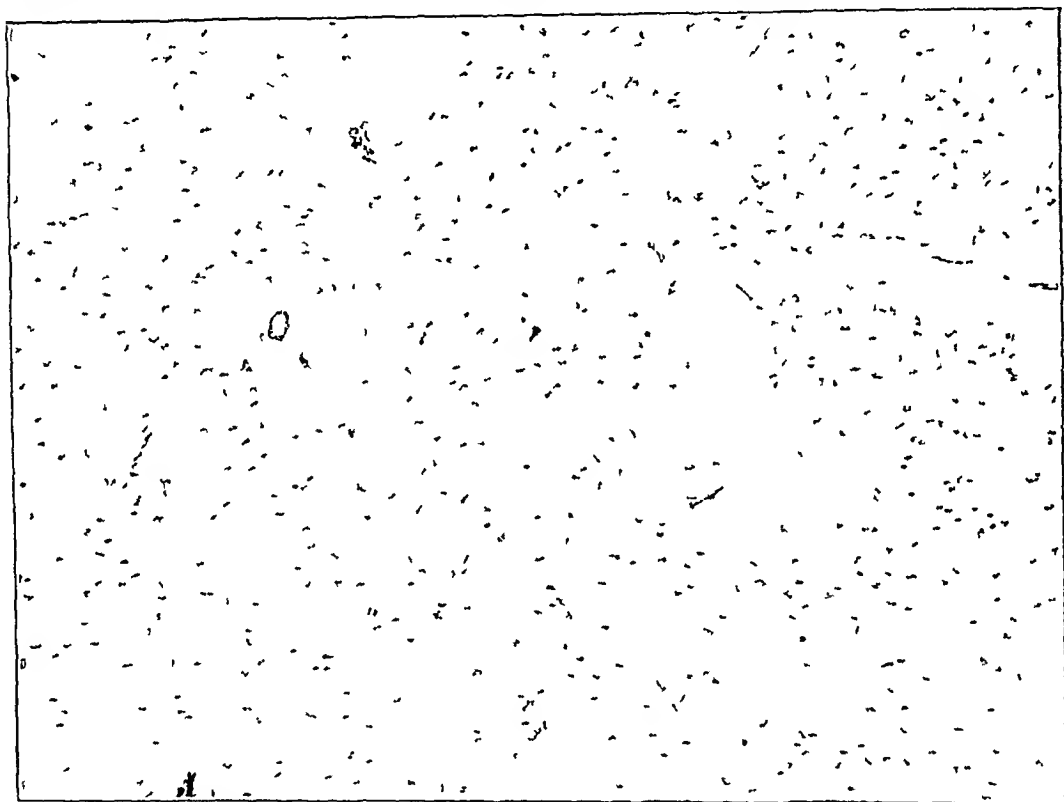


Fig 10—Juvenile paralysis agitans of twenty-five years' duration. Section through the putamen. Toluidin blue, $\times 384$. Note the increase of glia nuclei and almost complete absence of the large pallidal cells. The small ganglion cells are not reduced in number.

medullary layer. The ansa system, namely, the strio-hypothalamic radiations, also showed some thinning and atrophy of its fiber systems.

These alterations in the medullary network and radiations of the corpus striatum were diffuse and not sharply defined. They were nevertheless unmistakably present.

The evidences of chronic cellular atrophy in the neostriatum were quite definite and distinct and because of their chronic character could not have been the result of pyrexia or of the terminal infection to which both patients succumbed.

The motor cells of the corticospinal system were quite intact. The large cells of Betz in the rolandic area were well preserved, as were also the large multipolar cells of the anterior horns of the spinal cord. Furthermore, there were no evidences of atrophy or sclerosis of the pyramidal tracts either in the brain or in the spinal cord.

With the exception of pathologic changes in the efferent pallidal system noted above, namely, chronic atrophy of the giant pallidal cells of the neostriatum, a reduction in the fiber network of the globus pallidus and atrophic thinning of the fibers of the ansa system, the central nervous system appeared normal.

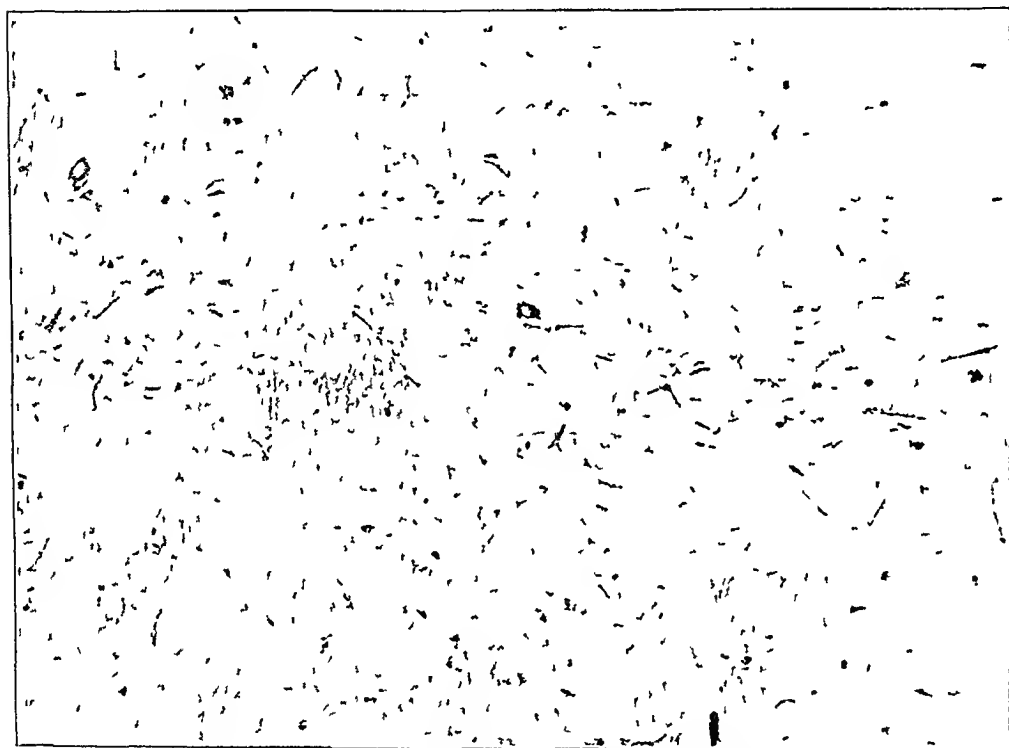


Fig 11—Juvenile paralysis agitans of twenty-five years' duration. Section through the globus pallidus. Toluidin blue, $\times 384$. Showing atrophy and diminution in number of the motor cells of the globus pallidus. Note the increase of glia nuclei and numerous irregularly formed concretions.

Histologic studies of sections from the cerebral cortex, the cerebellum, optic thalamus, pons, medulla and spinal cord revealed no lesions which could be offered as an explanation for the phenomena of the disease.

COMPARISON OF LESIONS WITH THOSE OF JUVENILE PARALYSIS AGITANS

It is not without interest to compare these pathologic changes with the histologic findings in juvenile paralysis agitans of twenty-five years' duration reported in my earlier monograph. In this case a study

of the central nervous system by modern histologic methods showed no lesions, excepting of the corpus striatum. In this region the cells of the globus pallidus type were diminished in number, the reduction estimated by comparative cell counts varied from one-sixth to one-half the normal. The greater number of the remaining cells were in various stages of chronic atrophy. These cellular changes were not confined to the cells of the globus pallidus proper, but were also evident in the globus pallidus cells of the caudate nucleus and putamen. The cellular atrophy was therefore confined to a single type of cell, namely, that of the pallidal type. This was apparent in the globus pallidus proper, also in the caudate nucleus and putamen—the neostriatum (Figs 10 and 11)



Fig 12—Juvenile paralysis agitans (Weigert-Pal method) Horizontal section through the cerebral peduncle and basal portion of the corpus striatum. Note the thinning of the ansa peduncularis.

There was also a moderate increase of the glia cells of the globus pallidus, and of the putamen and the caudate nucleus. There was, however, no increase of the glia fibers. This was regarded as a replacement manifestation, secondary to the atrophy of the motor neurons of the pallidal system. The blood vessels of the corpus striatum showed in certain areas a moderate thickening, there were no occlusions and no evidences of any serious vascular or perivascular disturbance.

Corresponding to the atrophy of the efferent cells of the pallidal system, there was a moderate thinning of the striohypothalamic radiations, namely, the lenticular bundle of Forel, the strio-luysian fibers

and the ansa lenticularis and peduncularis (Fig 12) This diminution was moderate in degree and was evenly distributed The medullary network of the globus pallidus also appeared to have undergone some slight diminution, but this was difficult to determine by the Weigert method, and, if present, it was evenly distributed and moderate in degree

The only discoverable lesion was a widespread atrophy and disappearance of the cells of the pallidal system, which I would regard as the essential motor or projection system of the corpus striatum

A certain harmony in the pathologic changes in the three cases of paralysis agitans therefore exists

In all, the cellular atrophy was limited to the large motor cells of the corpus striatum (pallidal system) with preservation of the small ganglion cells of the neostriatum (neostriatal system) In all, there were also evidences of atrophy in the ansa system—the strio-hypothalamic radiations with some reduction in the medullary network of the globus pallidus

The greater degree of involvement in the juvenile case I would explain by the longer duration of the malady, twenty-five years, in comparison to the two cases recorded in this paper in which the duration of the disease had not exceeded ten years The longer duration of the disease would account for the greater atrophy and diminution in number of the pallidal cells, the marked increase of glia nuclei and the cellular atrophy in the globus pallidus proper (paleostriatum) The evidences of atrophy in the motor cells of the globus pallidus proper in the two cases described in this paper were only slightly indicated by a somewhat doubtful reduction in size of the cell body and a slight rounding and angularity of outline as compared with normal cells, minor changes which would only have a significance taken in conjunction with the more marked changes in the neostriatum and the very evident alterations in these cells in the juvenile paralysis agitans case

There is, I believe, a certain analogy between the histologic findings in the corpus striatum in cases of paralysis agitans and those demonstrable in the precentral convolution of the rolandic area in cases of primary lateral sclerosis In this latter affection it was long held that the large motor cells of the cerebral cortex were not affected and that the lesion was confined to the more distal portion of the primary motor neuron which gradually progressed centripetally

Later investigations, however, have shown a considerable deviation from the normal which varies directly with the duration or severity of the disease These cellular changes may range from simple atrophy of the cell to complete destruction, there remaining only cellular rests and fragments

It is, I believe, not without significance that these two system diseases of central motor tracts should present variations in the degree of the cellular changes in harmony with the duration of the clinical picture, and that the character of the cellular changes should be essentially the same (abiotrophy)

THE SYMPTOMATOLOGY OF PARALYSIS AGITANS

The observations on symptomatology which are summarized in the following pages were carried out in the neurologic wards of the Montefiore Home and Hospital, the wards and outpatient department of the New York Neurological Institute and in my private practice during the past two years. Over fifty cases were utilized, representing various stages and types of the disease.

The symptomatology of paralysis agitans has been so thoroughly investigated by the most distinguished clinicians of the past and present that but little may be added in the way of new observations. The character of the paralysis, the tremor and the rigidity have all been carefully studied by Zingerle,⁸ Forster⁹ and many others, and the peculiar loss of the automatic and association functions of motility was especially emphasized by Zingerle.

My studies in the symptomatology are therefore in the main confirmatory of the results achieved by other observers, but approached from a new point of view, namely, that paralysis agitans is not a disease, but a characteristic type of central palsy resulting from a lesion in the pallidal system of the striospinal mechanism.

The cardinal symptoms of paralysis agitans are three in number, and consist of *paralysis*, *rigidity* and *tremor*. The great variation in the clinical picture is dependent on the extent of involvement of the musculature and the degree in which these three fundamental symptoms are present.

In the common form of the disease all three symptoms are usually present in combination, there being simply a tendency to gradual progression.

In other cases, especially in the earlier stage, one symptom may dominate the clinical picture or even be present alone, so that certain special types are recognized. For example, there is a rigid type, the paralysis agitans *sine agitatione*, and a rare *tremor type*, the paralysis agitans *sine rigiditate*. Of these two types, the rigid form is by far the more common and constitutes, in some of the larger

⁸ Zingerle Ueber Paralysis Agitans, Jour f Psychol u Neurol, 1909, 14, 81

⁹ Forster Ueber Koordinationsstörungen bei Paralysis Agitans, Berl klin Wchenschr, 1912, 49, 478

statistics, about 20 per cent of all cases, the disease running its course with little or no tremor manifestations

I would also emphasize the rare occurrence of what appears to be a pure *paralytic type* of paralysis agitans in which the typical paralytic disturbances are manifested without evidences of tremor or any noticeable rigidity. Of this type, I have only observed one case and a somewhat similar example has been recorded by Kramer¹⁰. This type, while rare, is of great interest, and may give rise to considerable diagnostic uncertainty.*

In this connection it is interesting to recall that Forster¹¹ has described paralysis agitans with hypotonia. In this case the characteristic paralytic disturbances with tremor were present, but without rigidity. Instead, there was a well marked hypotonicity of the musculature.

In this somewhat anomalous group of cases it is possible that we are not dealing with a true system disease, but a special vascular type with involvement of other systems, producing a condition similar to that which has been observed in certain *flaccid types* of hemiplegia.

THE PARALYTIC DISTURBANCES OF PARALYSIS AGITANS

The motor disability of paralysis agitans is dependent on the rigidity and a curious type of palsy, which differs from other forms of paralysis by reason of the nature of the paralytic phenomena. The paralysis is limited to the automatic and associated movements of the body and presents a striking contrast to the corticospinal type of palsy in which there is a loss of isolated synergic, or dissociated movements. It is for this reason that such motor activities as those concerned with

* REPORT OF CASE—*Paralytic Type of Paralysis Agitans*—A man, aged 62. Duration of the disease two years. Onset with slowness and weakness of movement, affecting first the arms and later the legs. Gradual progression with subsequent involvement of speech and gait. There is a slight masklike expression of face, the eyes are fixed and staring, speech is slow and monotonous. The gait is slow and shuffling, the arms do not swing rhythmically, but are held inertly by the side. There is no festination. There is no tremor and no rigidity of the musculature. The tendon reflexes are all present and active. The skin reflexes are present. (No Babinski sign.) Sensation is normal. The attitude, gait and facial expression are suggestive of paralysis agitans. There is infrequent winking, poverty of movement, and great difficulty in rising from a sitting posture. There is an absence of the associated movements of extension of the wrist on making a fist (absence of the normal *extensor kick of wrist*), which is so characteristic of this form of palsy. The patient was examined three months later and the above findings confirmed. There was a paralysis of automatic and associated movements of the paralysis agitans type without tremor or rigidity.

10 Kramer. Paralysis Agitans ähnliche Erkrankung, Berl klin Wchnschr, 1914, **51**, 1287, Neurol Centralbl, 1914, **33**, 729.

11 Forster. Paralysis Agitans mit Hypotonie, Berl klin Wchnschr, 1913, **50**, 649.

walking, running, sitting, rising, lying and turning in the recumbent posture show such marked and early involvement

It is, I believe, largely for the same reason that there is so much delay and difficulty in initiating movements, as, for example, in rising from the sitting posture. In such movements the associated activities of massive muscle groups are impaired and it is only by great effort of will that the defective automatic function is replaced by corticospinal activity. The peculiar muscular rigidity is also a powerful factor in causing slowness and delay in the initiation of movement and will be discussed more in detail under the heading of rigidity.

If a fairly well advanced case of paralysis agitans is observed at rest, one is impressed by the unusual motor passivity of the individual. The expression of the face, as reflected by the muscles, does not change with variations of the mood. Such emotions as sorrow, joy, surprise and anger find their chief or perhaps only expression in the eyes. An apparent exception would seem to be the smile, as many cases of paralysis agitans are capable of a fairly bright smile. It is, however, a cortical smile and one that a normal person often simulates in a conventional way without any corresponding sensation of joy. These patients, however, are rarely capable of laughter, that is, good hearty laughter in the complete sense, with its complicated series of automatic and associated activities. One is also struck by the absence of the usual gestures and similar associated motor activities which automatically accompany conversation and social intercourse. Even an automatic act such as winking, which is to a large extent of reflex origin, is diminished in frequency, and infrequency of winking has long been recognized as a curious symptom of the disease.

The sufferer from paralysis agitans may be in a sorrowful mood, and the eyes not infrequently fill with tears, but sobbing or crying with all its manifold associated acts is but rarely observed, and practically never in the later stages of the disease. The same may be said of anger, the motor expression for which is generally impaired in tone of voice, facial expression and gesture.

This is also true of such complicated automatic acts as coughing and yawning, which are not manifested in their complete motor form in this disease and yet are unimpaired in the palsies of spastic or corticospinal origin.

In the act of *voluntary* coughing, which is often feeble, the associated contractions of the latissimus dorsi are occasionally absent.

Especially interesting for motor studies are those cases of hemiplegic type in which the paralysis and rigidity are strictly unilateral. In such a case it is possible to observe the normal play of facial expression on the unaffected side with well marked evidences of the

mask on the paralyzed side. It is usual to find under these circumstances that the nasolabial fold has disappeared and also that the slight creases of the forehead have faded from the paralyzed side showing in a slight degree the loss of this controlling mechanism for facial expression.¹

I have also noted in these unilateral types absence of the associated movements of the auricle on elevation and contraction of the brows and the frontalis muscle, a very suggestive loss, as such movement must be phylogenetically very old and therefore under striatal control.

The purely reflex act of swallowing is not generally impaired even in the last stages of the disease and we have observed quite advanced cases with complete anarthria and general rigidity when solid and liquid nourishment could be taken without great difficulty by means of the purely reflex mechanism of deglutition.

The same lack of motor association is often noticeable on looking toward the right or left. The eyes turn, but without the usual associated movement of the muscles of the neck which move the head conjointly with the movements of the eyes, also on looking upward, not infrequently the associated contraction of the frontalis muscle fails, in contrast to the normal associated movements which distinguish this act.

If an irritating or unpleasant odor is held before the nose, there is a withdrawal of the head, but the movement lacks the emotional expression of disgust or irritation both in the face and in general character of the withdrawal manifestations.

It may be added that while some of the above symptoms or, indeed, many of them, may be observed in advanced cases of the disease, it is not to be assumed that they are all present in any given case as the affection is but slowly progressive and the patient usually succumbs from some intercurrent disease long before his automatic and association motor mechanism is completely destroyed.

PARALYSIS OF ASSOCIATED MOVEMENTS OF THE ARMS

Very interesting defects in the association of movement are manifested in the upper extremities. For example, one of the earliest and most characteristic symptoms of the disease is the loss of rhythmical associated movements of the arms in walking. The patient with paralysis agitans walks with the arms held stiffly by the side.

* NOTE—I have elsewhere¹² expressed the view that the regulating center for the emotional innervation of the face is situated in the anterior portion of the corpus striatum and not in the optic thalamus as is held by many observers.

¹² Hunt, J. Ramsay. The Efferent Pallidal System of the Corpus Striatum. A Consideration of Its Functions and Symptomatology, *Tr Am Neurol Assn*, 1917, p. 10 (*Jour Nerv and Ment Dis*, 1917, 44).

Under normal conditions the arms swing alternately with the legs in walking or running, thus simulating the use of the forelegs in quadrupeds Dupré¹³ quite correctly interprets this phenomenon as a vestigial manifestation—a remnant in the biped of a more primitive quadruped gait

This rhythmical action of the arms in walking, running and jumping is lost comparatively early in the disease, and yet the ability to voluntarily swing the arms shows no impairment

Again, if the attempt is made to open the hand the fingers slowly unfold and extend but there is not the marked abduction of the thumb and spreading of the fingers which takes place normally, and if the hand is closed quickly, as in grasping an object firmly, the fingers flex and are folded into the palm, but without the sharp associated movement of extension of the wrist, which is present in every normal person (absence of the extensor kick)

It is of interest to recall that the phenomenon of simultaneous extension of the hand on making a fist is increased in spastic paralysis, the so-called "radialis phenomenon" of Strumpel, the absence of cortical inhibition in such cases permitting its more complete expression. It is an involuntary associated movement which permits of a firmer grasp of an object by elongating the points of insertion of the flexor muscles of the forearm. This movement together with the abduction of the thumb and spreading of the fingers are phylogenetically older movements which were of great importance in the "climbing period" of our ancestry, and which still subserve a useful function. (A similar mechanism may possibly underlie the spreading movements of the claws observed in cats.) This absence of the *extensor kick* of the dorsum of the hand is not only an important and early sign of paralysis agitans, but together with the absence of the alternating rhythmical swing of the arms in walking constitutes an important sign of other clinical types of pallidal palsy from focal lesions of the corpus striatum (Hunt)¹⁴

The loss of other forms of associated movements of the upper extremities are also occasionally observed, for example, the contralateral contraction of the erector spinae group on swinging the arms forward or on abduction of the arm to a horizontal position

PARALYSIS OF ASSOCIATED MOVEMENTS OF THE LEGS

In movements of the lower extremities a similar loss of muscle association may be demonstrated. In walking, for example, there

¹³ Dupré, Ernest. Origine Ancestrale et Signification quadrupède des Mouvements des bras dans la Marche humaine, XII Cong Internat d med, Moscow, 1897, 2, 82, Sect. Anat

¹⁴ Hunt, J Ramsay. Clinical Types of Paralysis Referable to the Pallidal System of the Corpus Striatum, Tr Assn Am Phys, 1918

is a failure of the associated flexion of the thigh, knee and foot, which accompanies the normal act. Instead, the foot hangs as the knee is lifted which gives the slow dragging movement and shuffling gait which is so characteristic of the disease. Such phenomena as propulsion, retropulsion and lateropulsion may be explained by the loss of the normal associations of movements between the leg and trunk muscles which are a part of the upright posture and the act of walking.

Another very interesting loss of associated movement may sometimes be observed in the lower extremities. Under normal conditions while lying in the recumbent posture if the attempt be made to elevate one of the legs, the effort is accompanied by a very distinct contralateral pressure of the heel of the opposite side against the floor or the bed. It is a contralateral associated movement which is of material assistance in the elevation of the extremities and has been utilized by Dr Hoover as a differential sign between the hemiplegia of organic and functional origin. This contralateral movement is absent in hysterical hemiplegia because of the absence of the psychic effort of innervation, it is, however, increased in the ordinary spastic hemiplegia of pyramidal tract origin. In paralysis agitans this phenomenon, however, is not infrequently absent, the contralateral pressure of the heel being absent or diminished because of the loss of normal association of movement. The absence of the contralateral pressure of the heel on elevation of a paralyzed extremity may be demonstrated very readily in some hemiplegic types of this disease.

PARALYSIS OF THE ASSOCIATED MOVEMENTS OF THE TRUNK

Very grave disorders of association are also to be observed in movements performed by the trunk muscles, probably because the most important function of these large muscle groups are concerned with automatic and associated movements. The trunk muscles are phylogenetically the oldest of the skeletal muscles, antedating in their origin those of the extremities. It is, therefore, not surprising to find a grave disorder of their function in paralysis agitans, a paralytic affection produced by the loss of the efferent motor neurons of the corpus striatum*. The disturbance of trunk movements are often disproportionately affected as compared with movements of the legs and upper extremities, especially the latter. The movements of the upper extremities unquestionably having a much closer relation to corticospinal or acquired movements than have those of the trunk.

* NOTE—On theoretical grounds it would seem to me probable that the trunk muscles because of their phylogeny are closely related to the globus pallidus or *paleostriatum*, while the muscles of the extremities including the head, are more closely correlated with the *neostriatum*.

It is often extremely difficult for cases of paralysis agitans to turn in bed, to sit up, or perform other simple movements of the trunk. On lying down they fall back, the legs rising helplessly in the air, there being no effort made to regulate this movement by extension of the thighs which would tend to counteract the tendency to roll backward with the legs in the air. Furthermore, on attempting to rise from the recumbent posture, with the arms folded on the chest the effort often fails as there is not the initial flexion of the hips and subsequent fixation of the lower extremities thus permitting the use of the ileopsoas muscles in elevation of the trunk. The patient falls backward, the legs rising helplessly in the air.

Very striking is the absence of association movements of the arm and shoulder muscles when the examiner offers his hand for the assistance of the patient while attempting to rise from the recumbent or sitting posture. The hand of the examiner is taken but is merely touched or is held very lightly in a perfunctory manner, and no energetic effort is made to utilize this additional source of aid. The patient rises but without any force being expended by the arm in an effort to assist by pulling or lifting. The absence of spreading and grasping movements of the hand is here manifested in a larger way by the inability to assist the massive movements of the trunk by pulling and lifting movements of the arms. It would seem as if the examiner's hand were taken simply as a matter of form or habit and the rising is accomplished without the slightest assistance therefrom. This is one of the striking examples of the peculiar type of motor palsy with which these cases suffer, and may be readily demonstrated in advanced and comparatively helpless types of the disease.

A similar defect may be observed on rising from the sitting posture. A quite helpless patient will try laboriously to rise from an armchair, without the use of the arms, or if the hands appear to be used it can readily be shown that this is only apparent and that no real pressure on the arms of the chair is exerted. Furthermore, such helpful associated movements as leaning forward and placing the heels well beneath the chair before making the attempt to rise, are entirely disregarded and the attempt is made under what to a normal person would be the most difficult mechanical conditions.

Also, on sitting down, this comparatively simple act is usually performed quite grotesquely by a patient with paralysis agitans, so that the fall is not broken, and they sit down hard, the legs tending to rise in the air as they fall back in the chair. This defect is due to the same lack of association of movement—the heels not

being first placed well beneath the chair and the arms of the chair firmly grasped, as would be the natural course of events in other types of motor disability

Perhaps, there is no more beautiful demonstration of the loss of this association mechanism than occurs if the patient while standing on a large mattress is quite suddenly pushed over. In advanced cases of the disease, the fall is passive and complete, and occurs without any of those muscular attempts to break the fall which are present in all other conditions of palsy, even in profoundly spastic states. The patient falls, silently and stiffly, like a marble statue and oscillates to and fro in the same manner as would any solid or immobile object.

PRESERVATION OF ACQUIRED MOVEMENTS IN PARALYSIS AGITANS

In striking contrast to losses in the sphere of the automatic and association activities of movement is the preservation of specially acquired movements of cortical origin. These are carried out quite correctly in every detail, except for the difficulties produced by the tremor, rigidity and the paralysis of associated movements. A case of shaking palsy which has lost the alternating rhythmical swing of the arms in walking, the spread of the fingers and abduction of the thumb, the extensor kick of the wrist and the other paralytic disturbances enumerated above will take off his coat, draw up a chair, pick up a pencil from the floor and proceed to write, all the movements being quite correct in their detail except for the rigidity and tremor.

The motor disturbances just enumerated, therefore, involve the associated and automatic movements. Motor activities which are phylogenetically old and which are automatic and involuntary in character. It is very likely that this form of motor activity had reached an advanced stage of development in the lower forms of life, and that further additions to the wealth and variety of motor activities coincide with the appearance and evolution of the cerebral cortex.

This older mechanism which governs the association of movement retains, however, its full activity in man and is utilized in many, if not all, cortical movements. It would be difficult to conceive of any but the simplest motor acts of cortical origin in which the older mechanism does not play some rôle. Many acquired movements subsequently become more or less automatic, as for example, brushing the teeth, shaving with a safety razor, hammering, etc. Such acquired activities are not infrequently lost or seriously disturbed early in the

course of paralysis agitans, probably because of the preponderant automatic component of striatal origin *

RELATIONS OF THE CEREBRAL CORTEX AND THE CORPUS STRIATUM

The nature of the mechanism by which the cortical and striatal activities are harmonized is largely speculative. It now appears highly probable that the corpus striatum has no direct connection with the cerebral cortex. The pyramidal tracts, however, as they traverse the striatum send off numerous collaterals to all parts of this structure, so that a certain relationship between the motor cortex and the corpus striatum could be maintained through the medium of such collateral fibers. The optic thalamus also stands in very close relationship with all portions of the cerebral cortex by its afferent and efferent fiber systems, and as very close intimate associations exist between the thalamus and the corpus striatum the influence of the cortex on the striatum could be exercised in this manner.

In order that a structure should play the rôle which I would ascribe to the corpus striatum, it must have very intimate connection with the proprioceptive system and the cerebellum. Such a relationship surely exists for the corpus striatum through its very close association with the optic thalamus which has such direct and important connection with both the cerebellum and the general sensory system. I assume, therefore, that the motor system of the corpus striatum is essential for the control of automatic and associated movements, and that it exercises this function through the medium of the rubrospinal system and other extrapyramidal motor tracts which as yet are but imperfectly understood, the existence of which, however, cannot be denied.

IMPORTANCE OF THE EXTRA PYRAMIDAL SYSTEM IN MOTILITY

The importance of the extrapyramidal system is shown very beautifully in the development of motility in the fetus. At the eighth month

* NOTE—Realizing the peculiar nature of the motor disturbance in this disease, I have made some systematic efforts to restore by *reeducation* the loss of the more important automatic and associated movements. Attempting to substitute a cortical activity for the loss of the striatal mechanism. The difficulties are very great because of the very nature of the lost movements, their involuntary and automatic character.

However, something may be accomplished by substitution for the more important movements. The principle of this form of reeducation is to teach the patient the manner in which such movements, as rising from a sitting posture, sitting down, walking, turning, etc., are performed so that the victims of this disease may gradually acquire consciously what they previously performed unconsciously and automatically.

of fetal life Van Gehuchten¹⁵ has shown that the spinal cord contains no pyramidal tract fibers, the axis cylinders not yet having descended below the level of the pyramidal decussation of the medulla oblongata

Hence all nerve impulses to the muscles of the extremities before the eighth month of fetal life must pass by way of other motor tracts, namely, the extrapyramidal system

If we observe an infant born prematurely at the seventh month, one cannot but be impressed by the variety and strength of movements which show the characteristic qualities of striatal motility. The early myelination of the ansa system of the corpus striatum which appears about the fourth month of fetal life, therefore, acquires a new significance in the light of the more active fetal movements which begin at this period and their probable striatal origin

In conclusion, it may be stated that this very complicated strio-spinal mechanism in man finds a very simple counterpart in the lower forms of life and is represented by the globus pallidus (paleostriatum), the basal forebrain bundle of Edinger, and the primary motor fasciculus of the spinal cord. These structures constitute the primitive motor system of fishes which have only a rudimentary cerebral cortex and yet are endowed with a rich capacity for automatic and associated movements

THE RIGIDITY

A conspicuous symptom of paralysis agitans and one which contributes very materially to the general motor disability is the rigidity. Stiffness of the musculature is a large factor in producing that slowness of movement which with loss of the automatic and association activities of muscles cause the peculiar facial expression, attitude and gait, which are so characteristic of the disease

This rigidity is unquestionably of central origin, as is the spasticity which characterizes the paralysis of pyramidal tract disease. It, however, presents certain differences, the explanation for which will be offered later

The muscles are quite firm to touch, their contour is well defined and there is a state of continuous hypertonicity which gives to passive movements an impression of waxlike rigidity. In this respect the hypertonia of paralysis agitans differs from that of spastic paralysis. It is more plastic, while that of the spastic state is more elastic in character. Passive movements in paralysis agitans show that the continuous rigidity is often broken by a peculiar rhythmical sensation due to an intrinsic *tremor tendency* of the muscle substance. This

15 Van Gehuchten. Faisceau Pyramidal et Maladie de Little, Jour de neurol et d'hypnol, 1896, 1, 225

muscle manifestation, or cogwheel rhythm as it is sometimes called, is more apparent in those forms of the disease in which tremor is well marked and, when present, is a very characteristic sign

Both forms of hypertonicity, spasticity and rigidity are increased by irritation of the skin, by cold and by mental excitement, both are diminished by rest, warmth and sleep. The spastic state is further characterized by certain clonic phenomena and exaggeration of the tendon reflexes. In paralysis agitans, muscle clonus and reflex hyperexcitability are absent, except for occasional pseudoclonus or tremor clonus in the earlier stages of the disease. In the spastic state, however, a certain elastic quality of hypertonicity is more in evidence. In the rigidity of paralysis agitans the plastic component predominates — and this constitutes the chief difference between these two forms of hypertonus.

It is generally held that the hypertonicity of spastic states is caused by a loss of the cerebral inhibitory function and when the connections between the motor cortex and the motor cells of the spinal cord are severed, spasticity results. It would thus appear that a higher motor center in order to be effective, must control the spinal mechanism which is engaged in the regulation of tonus, and when this control is lost hypertonicity results. A similar explanation may be offered for the occurrence of rigidity in paralysis agitans.

According to my conception, this disease is the result of an atrophy of the essential motor projection system of the corpus striatum — the pallidal system, which exercises a controlling influence on the lower spinal mechanism through the medium of the extrapyramidal motor tracts.

As the corpus striatum represents a higher controlling motor mechanism, although phylogenetically much older than the corticospinal system, it also must control or inhibit spinal tonus, and when this inhibition is lost, hypertonicity of the musculature results.

There are certain peculiarities in the quality of this hypertonicity which I would ascribe to differences in the relationship of the corticospinal and striospinal systems to the peripheral nerve distribution and the constituents of the muscle fiber (Hunt¹⁶).

THE INTRINSIC CONTRACTILE SYSTEMS OF STRIATED MUSCLES AND THEIR DUAL INNERVATION

The voluntary musculature of the body belongs to the group of striated muscles which is composed of two distinct substances or

¹⁶ Hunt, J Ramsay. Preliminary Report on the Evidence Indicating the Existence of a Paleokinetic and Neokinetic System for the Transmission of Motor Impulses in Peripheral Nerves, Tr Am Neurol Assn, 1918

systems The one is the anisotropic disk system which is innervated by the large multipolar cell of the anterior horn, a medullated nerve fiber and the motor end plate of the muscle, the other is the sarcoplasmatic substance which is under the control of the sympathetic system and is innervated by the sympathetic motor cell of the anterior horn, nonmedullated nerve fiber and the terminal sympathetic end-plate of the muscle fiber

These two muscle systems differ essentially in their histologic, physiologic and chemical characteristics, and each has a separate nerve supply and source of innervation The anisotropic disk system subserves the function of the twitch or quick contraction and is the predominant factor in the production of voluntary movements The sarcoplasmatic system, on the other hand, subserves a more plastic function and is especially active in automatic and association movements requiring fixed postures and attitudes Both components, however, the contractile and plastic, participating in all forms of motility, differing only in degree (Sherrington¹⁷ and Langelaan¹⁸)

The nonstriated, or smooth muscles of the body are innervated exclusively by the sympathetic nervous system and phylogenetically represent a much older system than that of the striated muscles It is, therefore, not altogether surprising that the striospinal system which controls a lower grade of movement than the corticospinal should show the predominant rôle of the plastic component in contrast to spastic states, with their characteristic clonus and exaggeration of the tendon reflexes, which are manifestations of the contractile components of this form of hypertonicity

The higher development of motion is therefore attended by a greater activity of the elastic component, which thus permits of a more rapid and more complete control of motor activity In cortical movements, the anisotropic disk system is therefore the predominant factor

The evolution of the central nervous system has taken place by a gradual grouping and integration of lower segmental activities under the control of a higher regulating mechanism For example, in the realm of motility the simple reflex movement of segmental origin has been gradually replaced by the more complicated types of movements represented by automatic and associated acts of striatal origin Subsequently the isolated or dissociated movements of cortical origin were superadded which find their expression in the various acquired motor activities of man In this method of development a lower

17 Sherrington, C S Postural Activity of Muscle and Nerve, Brain, 1915, **38**, 191

18 Langelaan, J W On Muscle Tonus, Brain, 1915, **38**, 235

mechanism and its more limited forms of movements are not lost, but merely subordinated. All are utilized in that wonderful harmony of perfect movement, yet, underlying this are the various controlling and integrating mechanisms which remain as permanent landmarks of the slow and devious stages of the evolutionary process.

It is, therefore, not unreasonable to infer that the two intrinsic muscle systems of the striated muscle fiber with their dual innervation are under the control of separate correlating centers. The sarcoplasm with its sympathetic innervation differs so fundamentally in its neural, clinical and histologic characteristics from the anisotropic disk system that the probability of a separate controlling mechanism can hardly be questioned.

I would, therefore, postulate the existence of two distinct correlating centers for the control of the striated muscular system, one related to the nonmedullated system and the sarcoplasmic substance of muscle, the other related to the cerebrospinal medullated system and the more highly specialized contractile or anisotropic disk system of muscle.

Both centers are, I believe, under the control of the efferent pallidal system of the corpus striatum. The loss of the inhibitory influence of the motor cells of the corpus striatum in paralysis agitans would release these lower centers from control with the *static* symptoms so characteristic of the disease, namely, tremor and the rigidity. The tremor follows the release of the inhibitory mechanism governing the anisotropic disk system, the rigidity follows the release of the center controlling the sarcoplasmic substance of muscle. Generally, both tremor and rigidity occur in the symptomatology of the disease. However, in quite a considerable proportion of cases (in some statistics as high as 20 per cent) rigidity occurs alone, and it is by no means unusual to observe cases of paralysis agitans which throughout their entire course extending over a period of many years have manifested no evidences of tremor. The frequency of such an occurrence appears to furnish strong evidence for the assumption that two separate centers exist—one for the control of contractile, the other for the control of plastic tonus and which may be released independently in the course of the disease.

It has long been held, following the teaching of Hughlings Jackson, that tremor is associated with and is really a part of the rigidity. As he so aptly expressed it, "Tremor is rigidity spread thin, and rigidity is tremor run together." In other words, there is no inherent difference between tremor and rigidity except one of degree.

It is quite true that in the course of paralysis agitans the evidences of tremor disturbance generally tend to diminish with the progress of the disease and the further development of the rigidity. This diminution I would, however, regard as partly mechanical in its origin, the waxlike rigidity and contractures of the musculature diminishing and blocking the tremor tendency precisely as it blocks the freedom of voluntary and associated movements.

Be this as it may, there stands opposed to the Hughlings Jackson theory the frequent occurrence of the rigid type of paralysis agitans, progressing without initial tremor in which the character of the rigidity does not differ in any respect from that which accompanies cases with well marked tremor. This theory then would not adequately explain all of the types and various manifestations of the disease. It would therefore seem reasonable to postulate the existence of two distinct centers for the control of the muscle tonus of striated muscles: one a *center for contractile tonus* which regulates the anisotropic disk system through the medullated nervous system, the other a *center for plastic tonus* which regulates the sarcoplasmic substance through the nonmedullated nervous system. Both of these tonus centers are under the control of the pallidal system of the corpus striatum, the loss of which may be registered by tremor or rigidity according to the system involved.

THE TREMOR

The third characteristic symptom of paralysis agitans is the tremor. This curious motor disturbance consists of an involuntary tremor movement, rhythmical in character, varying from three to five vibrations to the second. It continues during rest and is therefore spontaneous and not dependent on movement or posture. It is, however, in no sense an intention tremor as this term is used to describe a tremor. It often, however, shows the characteristics of an action tremor, increasing during the passage of the movement but diminishing or ceasing as the end of the passage of the movement is reached—as, for example, when the finger is carried to the tip of the nose. Like another involuntary motor manifestation—chorea—it may be exaggerated by incidental occurrences. For example, both are increased by mental excitement and by motor activity. Both usually diminish during mental and physical rest, both cease during sleep. There are apparent exceptions to this latter statement in severe cases or perhaps when sleep is not profound.

The tremor of paralysis agitans has the same *tempo* in all of the parts affected, and at times nearly all muscles may be involved, including even those of the vocal cords and eyeballs.

THEORETICAL CONSIDERATIONS ON THE ORIGIN OF TREMOR

Speculating on these various involuntary motor phenomena such as tremor and chorea, it has seemed to me not unlikely that the development of motility has followed a certain scheme in the evolutionary cycle, which may be summarized somewhat as follows. The earliest types of motility were represented by slow plastic movements of the sarcoplasm of reflex origin under the control of the sympathetic nervous system. Subsequently, with the development of striated muscles and the anisotropic disk system, the quick contractions of reflex origin followed under the control of the medullated or cerebro-spinal nervous system.

The next step in the development of motility was the ability to perform quick to and fro movements with its correlating and inhibitory mechanism. Later, the ability to perform associated movements was developed and last of all, the isolated and dissociated movements of cortical origin, each group of motor activities having its own controlling and inhibitory mechanism.

As these various integrations of neural development were superadded one on the other in the long process of evolutionary development, they were harmoniously welded together. Each mechanism having reached a certain stage of development probably remained stationary, the evolution of motility proceeding along other lines. In this manner, we would have a nervous system whose constituents, while welded together and acting harmoniously, represent successive and distinct stages of motor development.

A loss of any connecting link in this chain of motor groupings would be followed by certain characteristic symptoms. Each link as it is superadded would control or inhibit the previous group, as such control would be necessary if higher motor activities are to be performed.

A loss of the small association and inhibitory cells of the neostriatum (neostriatal system) as occurs in Huntington's chorea is followed by the choreiform movements which are characteristic of this disease. The loss of this inhibitory mechanism releases the pallidal system of the corpus striatum from control, and as a result we have the involuntary associated movements which characterize certain diseases of striospinal origin (Hunt⁷).

A loss of the *efficient pallidal system* as occurs in paralysis agitans, releases other lower controlling and inhibitory centers from control. One of these is the center for the control of contractile tonus and the anisotropic disk system of striated muscle. When this is released, a tremor results which is characteristic of shaking palsy, the

disk system falling into involuntary, rhythmical to and fro movements which is one of the more primitive forms of motility

The other is a center for the control of plastic tonus and the sympathetic system of muscles, and when this is released rigidity results

The tremor of paralysis agitans I would, therefore, regard as an involuntary form of motor activity, 'not dependent on the rigidity per se as was suggested by Hughlings Jackson, but produced by loss of the inhibitory function of the pallidal system on a lower mechanism governing rhythmical movements of the anisotropic disk system of striated muscles *

GENERAL SYMPTOMATOLOGY

The essential and characteristic symptoms of paralysis agitans are those which have just been considered, namely, a paralysis of automatic and associated movements, the waxlike rigidity and spontaneous rhythmical tremor. All of these symptoms I would refer to atrophic changes in the *pallidal system* of the corpus striatum

Paralysis agitans is, therefore, a special type of central palsy, due to a loss of function of the striospinal system, in contradistinction to spastic paralysis, which results from disease of the corticospinal system. It is properly speaking, therefore, not a disease but a characteristic type of palsy which may result from a variety of pathologic lesions

Among these may be mentioned such conditions as senile atrophy, vascular degeneration, and various gross lesions of the corpus striatum, for example, softening, hemorrhage, tumors, encephalitis and syphilis. In a recent study,¹⁴ I have directed attention to various clinical types of palsy referable to vascular lesions of the corpus striatum characterized by hemiplegia, monoplegia and diplegia of pallidal origin

Paralysis agitans may, therefore, be regarded as a characteristic type of central palsy which may be produced by a variety of lesions, and is properly speaking a syndrome and not a definite disease. Mémère's disease, which was so long regarded as a distinct affection, has been gradually resolved into a number of pathologic entities, this, I believe, will be the fate of Parkinson's disease. According to my

* NOTE.—The possible relation of a primitive tremor mechanism to early heat production in warm-blooded animals is not without interest. Barr and DuBois¹⁹ have recently shown in calorimeter studies that the reduction of body temperature below a certain point is immediately followed by algid tremors with corresponding increase of heat production and rise of temperature. In this connection it is also of interest to note that according to Zingerle there is a slight elevation of temperature in about 23.4 per cent of cases of paralysis agitans which may have some bearing on the subjective sensations of heat and flushing which are not uncommon in this disease.

¹⁹ Barr and DuBois. Metabolism in Malarial Fever, THE ARCHIVES INT MED, 1918, 21, 654

conception it is a syndrome, characterized by a special group of symptoms — paralysis, rigidity and tremor — but referable to various types of pathologic lesions and various disease processes

Many other symptoms associated with our textbook description of paralysis agitans also deserve consideration. These, however, are regarded as incidental or complicating factors and not essential to the diagnosis of palsy

As the vast majority of paralysis agitans cases occur in the advanced or senile period of life, many of which last into senility, it is not surprising that evidences of mental disturbance and deterioration are often associated with this disease

The same is true of certain sensory symptoms, which are rarely objective, which are probably referable to associated changes in the optic thalamus. To regard these symptoms as essential to paralysis agitans would be similar to regarding sensory symptoms complicating spastic forms of palsy as essential and characteristic. Such symptoms are referable to general pathologic processes and are not in any sense peculiar to paralysis agitans

The various secretory, vasomotor and trophic symptoms are neither constant nor characteristic, and are to be regarded as secondary and not primary manifestations of this form of palsy

I have already indicated the possible relation of increased body temperature to the tremor movements, and some of the vasomotor and secretory reactions may have a similar origin

In paralysis agitans, however, we are dealing usually with cases in advanced life and with other evidences of marked senility, so that the organic changes in the brain and spinal cord are always limited to the pallidal system

CONCLUDING REMARKS

My conception of the nature and symptomatology of paralysis agitans may be summarized briefly as follows

The clinical picture to which the term paralysis agitans is applied, represents a fundamental type of palsy referable to the motor system of the corpus striatum. This system originates in the large motor cells of the corpus striatum, namely of the *globus pallidus type*, and terminate in relation to the ganglionic structures of the hypothalamic region, that is, the thalamus, the corpus subthalamicum and the substantia nigra

These cells constitute the chief cellular content of the globus pallidus or paleostriatum (*paleopallidal cells*). They are also present in considerable number in the caudate nucleus and putamen or neostriatum (*neopallidal cells*). The neopallidal cells are of especially large size and constitute veritable giant cells, in this respect suggesting a certain analogy to the giant motor cells of the Rolandic area (area gigantocellularis—cells of Betz).

The efferent pallidal system of the corpus striatum is a mechanism for the control of automatic and associated movement, and exerts its function through the medium of the so-called extrapyramidal tracts, namely, the rubrospinal and other extrapyramidal motor systems.

The pallidal system of the corpus striatum may be involved in various types of pathologic processes. There is a *primary atrophy of the pallidal system*, senile atrophy and vascular lesions, gross lesions from hemorrhage, softening tumor—indeed, any pathologic process localized in the course of the pallidal system may produce some of the characteristic symptoms of paralysis agitans. In this respect, the conditions are similar to those of the corticospinal or pyramidal tract system in which various pathologic lesions may produce symptoms of spastic paralysis.

Paralysis agitans is, therefore, referable to a disorder of the striospinal system as spastic paralysis is referable to a disorder of the corticospinal system.

These conclusions are based on the pathologic findings in three cases of paralysis agitans, one of the juvenile type and two of the presenile type, in which definite evidences of selective atrophy were demonstrable in the motor cells of the pallidal system. Corresponding to the atrophy of motor cells there was some thinning and atrophy of the strio-hypothalamic radiations or ansa system.

As the strio-hypothalamic radiations contain abundant afferent as well as efferent fibers, the ansa system appears simply somewhat attenuated and does not present the definite histologic picture of atrophy as is observed, for example, in the pyramidal tracts where the fibers are all efferent and grouped in a compact bundle. Much more distinctive are the evidences of atrophy in the pallidal cells, which stand out quite clearly amidst the normal neostriatal cells of this region.

The characteristic symptoms of primary atrophy of the pallidal system are paralysis, rigidity and tremor. All other symptoms which are described in paralysis agitans I would regard as secondary, or as complications and associated with some special form of pathologic lesion.

The paralysis is characterized by a loss of automatic and associated movements, which are phylogenetically old and represent a lower form of movements than are those of cortical origin. For this reason, such activities as walking, running, rising from a sitting or recumbent posture, grasping, etc., show especial involvement.

The loss of certain automatic and association activities of the muscles of expression are clearly demonstrable in the face. The corpus striatum, therefore, contains the motor center for the emotional innervation of the face.

The rigidity and tremor of paralysis agitans are referred to a loss of striatal inhibition, the corpus striatum controlling muscle tonus as does the cerebral cortex. When this inhibitory function is abolished hypertonicity results.

As the striated muscle fiber has a dual innervation and function, a correlating center or group of centers for the control of these two systems is believed to exist. One of these controls the anisotropic disk system which subserves the function of the quick contraction or the twitch, the other controls the sarcoplasmic substance and the more plastic contraction of the muscle. It is thought that the independent occurrence of a *tremor* and a *rigid* type of the disease may be explained on the basis of this hypothesis.

We must recognize, therefore, in the central nervous system, three systems which subserve the functions of motility. A *segmental* system with its various reflex functions, the *striospinal* system with its control of automatic and associated movements, and the *corticospinal* system with its higher quality of discriminative and dissociated movements. All three systems represent different stages of evolutionary development, and all are concerned in the elaborate function of motility. Each system as it is superadded utilizes those of earlier development. Therefore, in nearly all movements these various components are represented, the degree of representation varying with the character of the movement.²⁰

²⁰ For complete bibliography consult chapter on Paralysis Agitans in Lewandowsky's Handbuch der Neurologie, Vol. III, pp. 931 and 956.

BOOK REVIEW

MEDICAL WAR MANUAL No 6 Authorized by the Secretary of War and under the Supervision of the Surgeon-General and the Council of National Defense Laboratory Methods of the United States Army, Compiled by the Division of Infectious Diseases and Laboratories Office of the Surgeon-General, War Department, Washington, D C Illustrated Philadelphia and New York Lea and Febiger, 1918 Price, \$1 50

The money value of medical service including sanitary work is hard to compute, but many clear headed people who know something about the situation believe that much of the cost of our share in the war will be made up within a short time by the increased efficiency of the medical profession. No country in any period has so well prepared the medical service of its armies, none ever put into execution such far reaching training of its medical officers. Most of these will ultimately return to civilian practice.

This little book expresses the spirit of the Army Medical Corps and furnishes the model for such aids to practical work as every house officer and every laboratory worker needs daily. It can easily be carried in the pocket. From the remarks on the "Responsibilities of the Laboratory" and the "General Rules for the Conduct of the Laboratory" to the last paragraph, the book is packed with sound and accurate matter. The reviewer is tempted to quote, but selection is difficult when there is so much excellence. How important is Rule 6 "Label every thing and do it legibly," and Rule 12 "Remember that it is as important to keep accurate records as to carry on accurate tests." In every section are numerous details such as experienced laboratory workers unconsciously use, but that are often unknown to many others. In the under-staffed laboratories of medical schools and civil hospitals such things are likely to be missed in personal teaching, but can be learned by careful use of this manual. The value of the work in places where books are necessarily few can be seen by noting that it contains not only all the most useful methods given in laboratory manuals, but also sections on the sanitary examinations of milk and water, examinations for poisons, purification of water supply, and methods of sewage disposal. Criticism is invited, but little has been found to criticize except minor details. The headings for methods might be better if made uniform. The mixture of bold face and roman, of center and side heads is sometimes confusing. Under blood staining on page 46, it is said that with Wright's stain "sometimes if the preparation looks very bluish and under the microscope the red cells have a greenish blue tinge, the proper pink color can be brought out by washing the smear quickly with a few drops of the original undiluted staining fluid." As given earlier, washing longer with distilled water will do the same thing better. In examining for amebas in feces it is said that "the specimen is fished with a large platinum loop." Considering the need of the government for platinum for other purposes it might be said that two wooden tooth picks serve just as well.

A wide use is predicted for the little volume and much satisfaction from its use.

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INTENSIVE STUDY OF FIFTY CASES OF NEURO-CIRCULATORY ASTHENIA

REPORT ON FIFTY CASES OF SO-CALLED CONSTITUTIONAL NEURO-CIRCULATORY ASTHENIA ¹

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With the recognition of a cardiac class for remediable military recruits after the elimination of the unquestionably unfit, the so-called constitutional cardiac neurotic presents an extremely difficult problem. We have attempted to study intensively fifty such cases taken from all varieties of military service-men deemed unfit for overseas duty and who, in contradistinction to the possible infectious and functional group, were selected because of the constitutional or pre-enlistment nature of their complaint. This so-called neurocirculatory asthenic who reports for military duty has not been subjected to the strain of early training, nor has he recently suffered severe infection. He has complained of cardiac distress for years. He is made of poor material that has been constantly irritated. His start in life is only fair at best, and therefore, with added external and internal irritation he becomes a poorly disciplined waster of nervous energy.

This group is particularly susceptible to external stimuli. These men have allowed themselves to spend their nervous energy so recklessly that they are constantly on the threshold of stimulation and any slight irritation, emotional or otherwise, pushes them over the border and they respond as recklessly as they have always been accustomed to. With this point in view we have not considered this condition a definite clinical entity. It just so happened that in the

* Submitted for publication Aug 13, 1918

business of sorting, these cardiac neurotics were grouped together. Knowing the external stimuli, an investigation was attempted to find and remove all foci of irritation of an internal nature. At the same time a system of exercise was adopted in which men passed from mild to higher grade exercises in conjunction with route marches of one to six miles with and without light and full pack. Five groups were established, and after three days the man was moved to a higher grade exercise under favorable circumstances along with games and competitive drills. At the outset it was impressed on the men that they were not patients, but men under strict military discipline. A competent drill sergeant lived with the men and became both their leader and adviser. Competition and special privileges, along with a certain amount of pride in the police of their barracks, soon brought out the best that was in them. With the men satisfied with their surroundings, doing work and playing games within their limit of tolerance, all external stimuli were easily controlled. At the same time the internal stimuli or foci of irritation were rigidly investigated. The accompanying tables attempt to analyze this situation, and prove that there are definite foci which tend to lower the man's nerve capital and increase the offensive force to a point far above his defensive. With graduated exercise and discipline we hope to build up this defensive force and eliminate the offensive by removal of all irritating foci both internal and external.

The following schedules present the plan of procedure and take a typical case through the entire course. The tables present summaries of our study of fifty cases of so-called neurocirculatory asthenia. We have attempted to analyze these cases after the method of Thomas Lewis¹ of England.

At present no attempt is made to draw sweeping conclusions from these studies, which are herewith presented as a preliminary contribution to the subject.

Past History—Prevalence of Past Infection—Measles, whooping cough and tonsillitis seem to have played the greatest rôles in the past history of the cases under observation. Gonorrhea, pneumonia, scarlet fever, rheumatic arthritis and typhoid are next in frequency, and it is to this group of diseases that 22 per cent of the patients date the onset of their present condition.

¹ Report of Medical Research Committee, Series No. 8. Reports on Soldiers Returned as Cases of "Disordered Action of the Heart" (D A H) or "Valvular Disease of the Heart" (V D H).

TABLE 1—TYPICAL CASE RECORD

CARDIOVASCULAR CASE RECORD NO

Name, X Y Z Rank, Pvt Co Regt Inf
 Age, 22 years Race, White Service (Yrs, 8/12)

Occupation, Farmer
 Invalided, in training

History—Family—Maternal uncle T B—Mother very nervous—Grandfather, cancer
 Past—Measles, pertussis
 Habits—No cigarets 4 Cigars 2 Pipes 0 Chews 3 Alcohol moderate
 Onset—Gradual, cause unknown
 Symptoms—Duration, 4 yrs No Repetitions, Three times Dyspnea, Yes Pain,
 Yes Palpitation, Yes Fainting, No Giddiness, Yes Sweating, No Flushing,
 No Cough, No Weakness, No Nervousness, Yes

Thyroid Gland—Tumor, No Tremor, Yes Exophthalmos, No Diarrhea, No

Cardiac Status on Admission Cardiac Status on Discharge

Thrills—None Thrills—None
 Apex Impulse—5th Space 90 cm M L Apex Impulse—5th Space 90 cm M L
 Borders—R 3d Space 30 cm M L Borders—R 3d Space 30 cm M L
 L 5th Space 105 cm M L L 5th Space 100 cm M L
 Sounds—Base, P 2 = A 2 Sounds—Base, Clear
 Apex, Clear Apex, Impure 1st apical
 Murmurs—Apex, None Murmurs—Apex, None
 Base, None Base, None

Exercise Test Exercise Test
 Standing Rate 84
 Recumbent Rate 84
 Rec after Ex Rate 96
 Rec 2 min Rate 84

Arrhythmia—Respiratory Arrhythmia—Respiratory
 Bld Pr—Systolic 144, diastolic 95 Bld Pr—Systolic 136, diastolic 84

Group Progress—Good, highest grade exercises well tolerated
 Weight, 6 Day Intervals—149, 154, 156, 154, 158, 154, 159, 154
 Date of Admission—5/15/18 Discharge—7/15/18 Observation Time—62 days
 Final Disposition—Unrestricted military duty
 Diagnosis—Neurocirculatory asthenia, constitutional

TABLE 2—TYPICAL CASE RECORD

CASE RECORD NO

Name—X Y Z Rank—Pvt Co — Regt — Inf

General Physical	Cardiac	Psychiatric
General Appearance—Free, well developed and tanned, dermatographia Lungs—Clear Abdomen—Negative Extremities—No cyanosis, hands clammy	R C D—Within limits Sounds—P 2 = A 2 Murmurs—None Exercise—Response fair Action—Rapid, regular	Negative Mental Age—Adult
Neurological	Ear—Nose—Throat	Dental
K K—Coarse tremor of tongue, hands extended	Ears—Negative Nose—Nasal spur Lt Throat—Tonsils hyper bi lateral 2+, pus present Trans—Negative Diag—Tonsillitis, chronic, suppurative	R-14, Dental alveolar abscess Indication for extraction Incomplete D A A—R 14 extracted Conductive anesthesia
Gastro-Enterological	Genito-Urinary	X-Ray
History—Physical examination, stool and stomach analysis, negative	Prostate—Normal	R U L U 20 30 L M 55 R L L L 40 100 Gastro Intestinal—Negative
Laboratory		
Blood	Urine	Stool
Hemoglobin—70% Red—7,184 000 White—6,600 Differential—Not indicated	Color—Light straw Appearance—Clear Reaction—Acid Sp Gr—1.022 Albumin—Negative Sugar—Negative Microscopic—Negative	Color—Dark brown Consistence—Solid Mucus—Negative Blood—Negative Microscopic—Negative
Wassermann—Negative	Prostatic Smear—Negative	

TABLE 3—RECONSTRUCTION SCHEDULES
U S ARMY BASE HOSPITAL, CAMP SHERMAN, OHIO

Daily Schedule for "Reconstruction" Hospital			
A M	6 00	First call	
	6 20	Fully dressed, police around ward	
	7 30	Breakfast, mop floors and clean up details	
	8 00	Exercises	
	9 00	Physical examinations, review marching order	
P M	11 00	Absolute rest on beds	
	12 30	Mess	
	1 00	Recreation	
	2 00	Exercises and route marches	
	3 00	Games	
	4 00	Police and clean up	
	5 00	Mess	
	6 15	Retreat	
	9 00	Taps—All lights out	
Schedule of Exercises Cardiovascular Reconstruction			
Group	Exercise	Time	Days
Group 1	1	15 min	3
	1A	30 min	3
Group 2	2	15 min	3
	2A	30 min	3
Group 3	3	15 min	3
	3A	30 min	3
Group 4	3A and 1	30 min at 1 mile	3
	3A and 2	30 min at 2 miles	3
	3A and 3	30 min at 3 miles	3
	3A and 4	30 min at 4 miles	3
	3A and 5	30 min at 5 miles	3
	3A and 6	30 min at 6 miles	3 without pack
Group 5	3A and 7	30 min at 6 miles	3 with light pack
	3A and 8	30 min at 6 miles	3 with full pack
Total 42 days			

TABLE 4—RECONSTRUCTION SCHEDULES
U S ARMY BASE HOSPITAL, CAMP SHERMAN, OHIO

Graduated Exercises of Cardiovascular Reconstruction			
Exercise 1			
Position	Exercise	Command	Count
Arms to thrust, raise	Raise and lower shoulders	Up, down	15 times
Arms to thrust raise	Shoulders back and forward	Front, back	15 times
Hands clasped back head	Head forward and back	Front, back	15 times
Hands on hips, place	Head twist, left and right	Left, right	10 times
Arms extended, raise	Clinch and open fist	1, 2	20 times
Arms extended, raise	Describe circles palms up	Back, front	1 min
Arms backward, cross	Quarter bend knee	1, 2	15 times
Attention	Breathing exercise, inhale and exhale	Arms forward, up, back, downward	10 times
Exercise 2			
Hands on shoulders, place	Thrust arms forward, sideward and upward	1, 2, 3, 4	10 times each
Arms backward, cross	Quarter bend forward	1, 2	10 times
Hands clasped back head	Head forward and backward	Front, back	15 times
Hands on hips, place	Raise on toes	1, 2	15 times
Hands on hips place	Extend leg forward, ankle high and knee high L and R	1, 2, 3, 4	15 times each
Hands on hips, place	Raise leg sideward L and R	1, 2, 3, 4	10 times each
Arms extended, raise	Describe circles	Back, front	1 min
Hands on hips, place	Raise knee to level L and R	1, 2, 3, 4	15 times
Attention	Breathing exercise, inhale and exhale	Arms forward, up, back, downward	10 times
Exercise 3			
Hands on shoulders, place	Arms forward, upward, sideward	Front, up, down	20 times each
Hands on hips, place	Full knee bend	1, 2	8 times
Hands on hips, place	Bow oblique to L and R	1, 2, 3, 4	10 times
Hands on hips, place	Bend trunk backward	1, 2	10 times
Hands over head, raise	Bend and touch toes	1, 2	8 times
Arms to thrust, raise	Step and strike obliquely to left and right	1, 2, 3, 4	15 times
Arms on hips, place	Extend leg forward, ankle high and waist high L and R	1, 2, 3, 4	10 times each
Hands on hips, place	Rotate head L B R	1, 2, 3, 4	10 times
Attention	Breathing exercise, inhale and exhale	Arms forward, up, back, downward	10 times

TABLE 5—PAST INFLUCTIONS

	No	Per Cent		No	Per Cent
Measles	46	92	Rheumatic arthritis	7	14
Pertussis	35	70	Typhoid	7	14
Tonsillitis	30	60	Diphtheria	4	8
Gonorrhea	13	26	Malaria	3	6
Pneumonia	12	24	Mumps	2	4
Scarlet fever	11	22	Meningitis epidemic	1	2

CAMP SHERMAN, OHIO. **CARDIO-VASCULAR RE-EXAMINATIONS**

DISPOSITION

30 PER 1000=3%

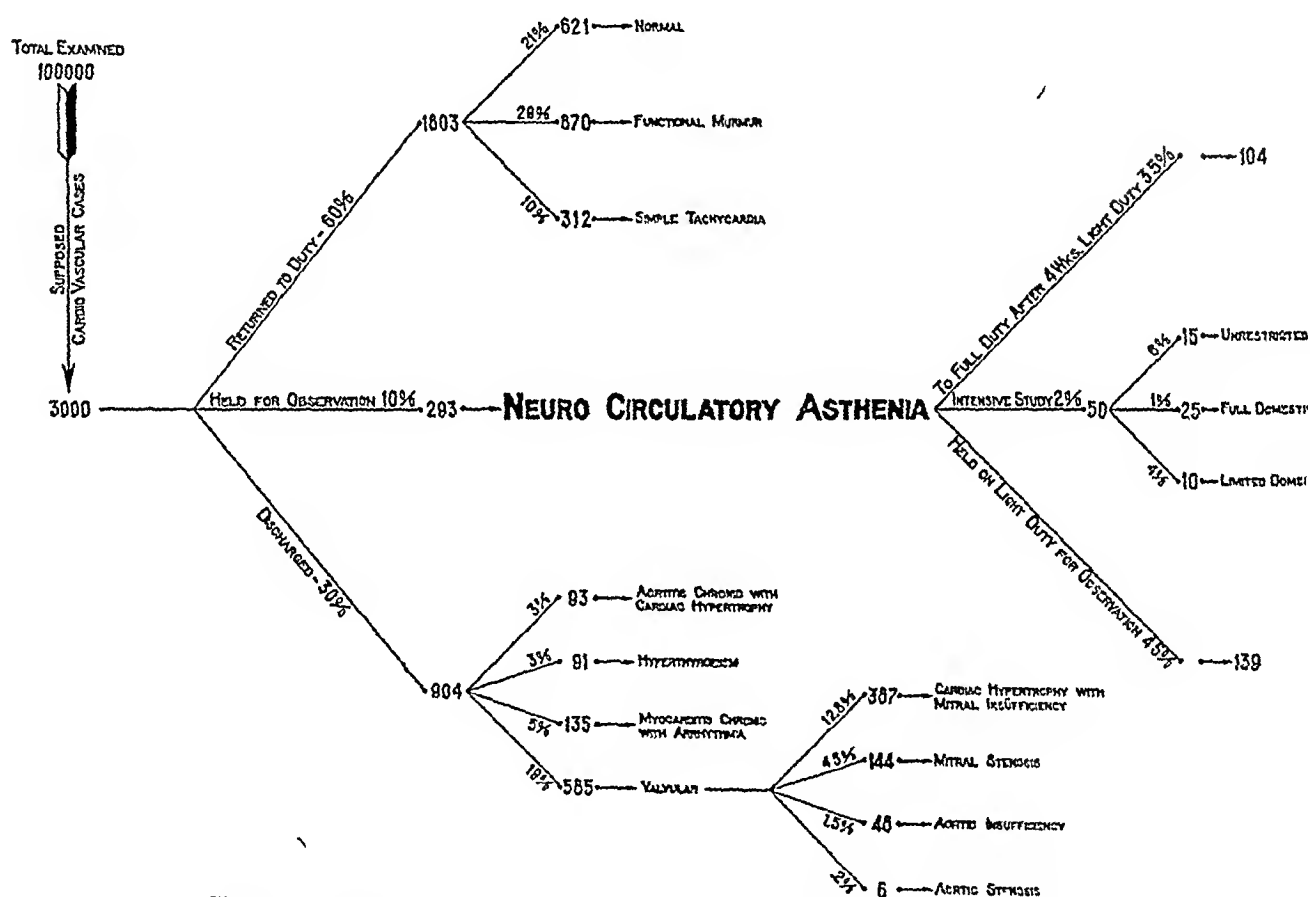


Chart 1—Results of cardiovascular examinations at Camp Sherman

Present Condition—Prevalence of Symptoms—Pain was the most frequent symptom complained of. The location of the pain was usually in the precordial region, at times in a well defined area, but again seemed to be a hyperalgesia of the chest wall. Dyspnea on exertion, paroxysmal palpitation, giddiness, nervousness, weakness, sweating and flushing were next in order of frequency of occurrence. *No one symptom predominated.* Precordial distress including dyspnea, pain and palpitation, nervousness, weakness and giddiness characterize the syndrome.

TABLE 6—PRESENT SYMPTOMS

	No	Per Cent		No	Per Cent
Precordial pain	44	88	Nervousness	22	44
Dyspnea	40	80	Weakness	22	44
Palpitation	37	64	Flushing	16	32
Giddiness	27	54	Fainting	5	10
Sweating	27	54	Cough	4	8

Previous Occupation—Civilian Life—A large portion of this class is drawn from those having sedentary or light occupations. Forty per cent of the group under study belong to this class. This percentage might even be increased to 53 per cent, since we list 13 per cent as farmers who call themselves such merely because they live on a farm and do light work.

TABLE 7—PREVIOUS OCCUPATIONS OF FIFTY PATIENTS

	No	Per Cent		No	Per Cent
Former—light work only	13	26	Engineer—stationary	1	2
Clerks	12	24	Engineer—civil	1	2
Mechanics	4	8	Attorney	1	2
Carpenters	3	6	Contractor	1	2
Electricians	2	4	Merchant	1	2
Illustrators	2	4	Jeweler	1	2
Coal miners	2	4	Optician	1	2
Laborers—common	2	4	Barber	1	2
Printer	1	2	Bartender	1	2

TABLE 8—MILITARY SERVICE WHEN INVALIDED (FIFTY PATIENTS)

	No	Per Cent		No	Per Cent
Infantry	35	70	Artillery—heavy	2	4
Machine gun	7	14	Signal—field	2	4
Quartermaster	2	4	Engineers	2	4

Onset of Symptoms—The patients' statements as to onset, cause and duration of symptoms are rather indefinite. Twenty-two per cent gave a history of a sudden onset and these dated their condition from some previous illness, although this entire group had been more or less nervous and below par since childhood. In 78 per cent the onset was gradual and the majority of these could give no definite reason or cause for their present condition. In most cases repetition of symptoms occurred with exercise, many others were due to emotional disturbances, and the remainder persisted constantly.

TABLE 9—OCCURRENCE OF SYMPTOMS

	No	Per Cent		No	Per Cent
Onset—sudden	11	22	Ascribed Cause of Onset—		
Onset—gradual	39	78	Patients' Statements		
Repetition—with exercise	25	50	Malaria	1	2
Repetition—with emotion	10	20	Railroad accident	1	2
Repetition—constant	15	30	LaGrippe	2	4
Ascribed Cause of Onset—			Typhoid	2	4
Patients' Statements			Pneumonia	2	4
Cause unknown	31	62	Scarlet fever	1	2
Overwork—sudden strain	5	10	Gonorrhea	1	2
Overtrained	2	4	Bronchitis	1	2
Overheated	1	2			

Duration of Symptoms—Forty-seven out of the fifty cases under observation gave a history of nervousness and cardiac distress previous to induction into military service. Development of symptoms followed scarlet fever in one case and the severe strain of overtraining in two cases.

TABLE 10—DURATION OF SYMPTOMS AND YEARS OF SERVICE

Average Duration of Symptoms					
Years	No	Per Cent	Years	No	Per Cent
20	2	4	6	6	12
18	1	2	5	5	10
16	2	4	4	4	8
13	1	2	3	11	22
10	6	12	2	3	6
9	1	2	1	1	2
8	2	4	1/4	1	2
7	2	4	1/12	2	4

Average Years Service when Invalided					
Years	No	Per Cent	Years	No	Per Cent
9/12	2	4	4/12	1	2
8/12	14	28	3/12	2	4
7/12	8	16	2/12	8	16
6/12	1	2	1/12	13	26
5/12	1	2			

General Physical Status—The majority of this group showed vasomotor instability as evidenced by alternating flushing, pallor, cold, cyanotic, clammy extremities and marked evidence of dermatographia. Fifty-two per cent were robust and well developed, while 40 per cent were rather slender, flat-chested and showed poor muscular tone. One man had a right side empyema following pneumonia. Examination of the lungs showed no evidence of structural change.

TABLE 11—GENERAL PHYSICAL STATUS

	No	Per Cent		No	Per Cent
Well developed	26	52	Lungs—empyema scar	1	2
Poorly developed	20	40	Congenital asymmetry (face)	1	2
Dermatographia	40	80	Cyanotic extremities (clammy)	40	80

Cardiac Status—No one in the entire group presented evidence of structural cardiac change. The relative cardiac dulness was constantly within normal limits. Twenty-two per cent had functional apical murmurs, while 28 per cent had accidental pulmonic systolic murmurs. Two men showed impure first apical sounds, while two had a reduplication of the first sound. The response to exercise was fair in 40 per cent, good in 50 per cent and poor in 10 per cent. The exercise test was "One hundred hops on the left foot." Ten per cent of the men had an apical systolic thrill palpable after exercise or excitement. A respiratory arrhythmia more marked in some than in others was present in all cases.

TABLE 12—CARDIAC STATUS

	No	Per Cent
Relative cardiac dullness within normal limits	50	100
Murmurs Functional apical systolic	11	22
Accidental pulmonic systolic	14	28
Sounds Impure first apical	2	4
Reduplication first apical	2	4
P-2 greater than A-2	17	34
A-2 greater than P-2	8	16
Response to Exercise Fair	20	40
Good	25	50
Poor	5	10
Action Rapid	44	88
Arrhythmia—respiratory	50	100

Thyroid Status—Twenty per cent of the cases under observation presented thyroid tumor to a greater or less degree. This is not unusual appearing in men drawn from the Ohio Valley region. Tremor was present in 96 per cent of the group, and a mild degree of exophthalmos appeared in 6 per cent of the cases. History of diarrhea was not elicited. Little importance is attached to these findings as a possible factor of causation of the syndrome under discussion.

TABLE 13—THYROID STATUS

	No	Per Cent		No	Per Cent
Tumor	10	20	Exophthalmos	3	6
Tremor	48	96	Diarrhea	0	0

Ears, Nose and Throat as Foci of Irritation—The nose and throat seem to yield the largest number of portals of entry for irritation and infection. Of the group under study the tonsils are the worst offenders, 90 per cent having chronic suppurative tonsillitis. Thirty-two per cent of the men showed deviation of the nasal septum, 20 per cent chronic sinusitis, while 8 per cent gave evidence of otitis media.

TABLE 14—STATUS OF EARS, NOSE AND THROAT (FIFTY CASES)

	No	Per Cent		No	Per Cent
Ears Otitis media, chronic,			Sinuses Chronic sinusitis	10	20
suppurative	4	8	Throat Tonsillitis, chronic,		
Nose Deviated septum	16	32	suppurative	45	90

Teeth and Mouth as Foci of Irritation—The teeth and mouths of the men under observation showed evidence of recent dental attention, in fact, 66 per cent of the group presented no evidence of oral infection. Thirty-four per cent gave positive findings of a degree indicating extraction. Following this procedure and after cleaning up the mouth infection, a definite, marked improvement was observed, not only in general conditions, but a specific beneficial result was noted in the heart rate and character of the response to exercise. This is in accord with the view that systemic irritation results more frequently from nonencapsulated granulomas on the apices of teeth than from definitely encapsulated blind abscesses. All cases under observation show the former condition.

TABLE 15—ORAL INFECTIONS (FIFTY CASES)

	No	Per Cent		No	Per Cent
No evidence of oral infection	33	66	Dental alveolar abscess	3	6
Gangrenous pulps	3	6	Carious roots	11	22

Genito-Urinary Status — All patients under observation denied syphilis, while 24 per cent (twelve in the group of fifty) admitted gonorrhea. Of the Wassermanns made on 11 cases, only two (or 4 per cent) were returned positive (++) These men were immediately subjected to rigid antisyphilitic treatment.

No man presented an active gonorrhea. Rectal examination of the prostate showed 10 per cent to be soft and slightly enlarged, 10 per cent moderately enlarged, 6 per cent small and nodular, the remainder normal. Only one case presented a tender and enlarged right seminal vesicle. Smears made of the expressed secretions following prostatic massage were all negative, no gonococci being demonstrated.

Urine Analysis — Routine urine examination failed to reveal any unusual findings, the few ordinary tests made being negative. An occasional trace of albumin appeared following heavy marching, but was only of a temporary nature.

Blood Counts — Average blood counts made on the fifty men showed very little of interest. The average red count was about 5,190,000, white count 8,700, hemoglobin 90 per cent. This ratio persisted through training. Ten cases showing low hemoglobin percentage on admission, after two months forced feeding and graduated exercises showed marked improvement and higher hemoglobin percentage, approaching normal on discharge.

Foci of Irritation—Psycho-Neurotic Factors — Psychiatric and neurologic investigations made on the group under observation yielded the data given in Table 16.

TABLE 16—PSYCHIATRIC AND NEUROLOGIC DATA

Family History	Per Cent	Personal History	Per Cent
Nervousness	72	Previous nervousness	64
Alcoholism	10	Alcoholic excess	4
Insanity	2	Psychasthenia	8
Epilepsy	2	Neurasthenia	4
Tuberculosis	36	Epilepsy	0
Carcinoma	8	Tobacco excess	10
		Head injuries	4

Definite evidence of psychasthenia was obtained in four men, one of whom was a religious fanatic. Two were definite neurasthenics, while four showed positive neurologic findings. The mental age was taken of each case in order that a more definite status might be established. Fifty-six per cent of this group measured normal adult mentality, while 44 per cent ranged from 8 to 15 years of age.

TABLE 17—COMPARING AGE WITH MENTAL AGE

Age, years	Per Cent	Mental Age*	Per Cent
33	2	Adult	56
32	2	15	6
31	2	14	6
30	8	12	16
29	6	11	2
28	4	10	6
27	4	9	4
26	12	8	4
25	14		
24	14		
23	12		
22	18		
21	0		
20	2		

* Binet combined point—Yerkes
Bridges scale

In the group under observation it so happened that we were able to study the syndrome under discussion in twins. These men were 22 years of age, well developed and farmers by occupation. The family history showed the mother to be very nervous. The men said they had been nervous since childhood, one dating the onset of symptoms four years, the other sixteen years previously. They served in different regiments and when invalided the one had had three-twelfths year, the other eight-twelfths year training. After completing the course of graduated exercise, both showed marked improvement and were returned to full duty. These two men were not malingering. Indeed, they were most anxious to return to full military duty. Both were of normal mental age, but had since childhood labored under the impression that they were definite "cardiacs." Examination revealed no evidence of structural cardiac change. After cleaning up their very bad mouth and tonsil condition, regulating the diet and graduating their exercise, these men are now rather formidable soldiers, doing full military duty.

Their improvement is shown in the accompanying table (Table 18). Heart and respiratory rates with blood pressure readings were taken before and after treatment.

TABLE 18—SHOWING IMPROVEMENT OF TWINS ON GRADUATED EXERCISE *

	Pulse		Respiration		Blood Pressure, Systolic		Blood Pressure, Diastolic		Return to Normal Minutes
	Before	After	Before	After	Before	After	Before	After	
D C on admission	108	144	16	18	140	170	90	90	3
D C on discharge	80	104	15	16	124	136	84	84	2
D L on admission	116	150	16	18	144	160	94	96	3½
D L on discharge	80	116	16	17	136	140	96	94	2

* Record of twins aged 22 years. Duration of symptoms 4 and 16 years. Mother very nervous. Exercise used, 100 hops on left foot. Observations made before and after.

Gastro-Intestinal Status—(Report by Capt Robert McCaughey)—The fifty men were asked if they believed themselves to have any stomach or bowel trouble. Forty-four—88 per cent—answered in the

negative Six—12 per cent—made positive declarations As to past stomach or bowel troubles thirty-eight—76 per cent—reported negative, twelve—24 per cent—positive

		Declaration					
		Present		Past			
Positive	Negative	Positive	Negative	Positive	Negative		
6	12%	44	88%	12	24%	38	76%

History and examination showed that twenty-five (50 per cent) were free from gastro-intestinal irritation, and the same number were found to have definite histories and findings of such trouble Of these twenty-five positive gastro-intestinal cases, seven (14 per cent) had intestinal stasis of the atonic type, one (2 per cent) of the spastic type, and one (2 per cent) had periodic stasis as shown by the history Three (6 per cent) had intestinal stasis associated with gastric atony, nine (18 per cent) associated with chronic inflammation Secondary or primary gastric irritation was found in four (8 per cent) of the group studied

TABLE 19—GASTRO-INTESTINAL STATUS

	No	Per Cent
Positive gastro intestinal cases	25	50
Intestinal Stasis		
Atonic type	7	14
Spastic type	1	2
Periodic type	1	2
Associated with gastric atony	3	6
Associated with chronic inflammation	9	18
Secondary-primary gastro intestinal irritation	4	8
Total	25	50

50 cases studied

TABLE 20—INTESTINAL STASIS

Number	1	2	3	4	5	6	7	8	9
Name	B J	G J	C F	M J	E M	G H	M W	K W	U O
Declaration, present	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Pos
Declaration, past	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Pos
History	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
Stomach empty	4½ hrs	4½ hrs	5 hrs	5 hrs	4½ hrs	6 hrs	6 hrs	6 hrs	6 hrs
Greater curvature	Crest	Crest minus 1 inch	Crest plus 1 inch	Crest minus 1 inches	Crest minus 2 inches	Crest minus 5 inches	Crest minus 2 inches	Crest plus 1½ inches	Crest
Transverse colon	Low	Kink	Kink	Low	Low		Kink Low		
Intestinal tract empty	72 hrs	96 hrs	96 hrs	96 hrs	72 hrs	72 hrs	72 hrs	48 hrs	24 hrs
Lumen of colon	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Spastic	Normal
Type	Atonic	Atonic	Atonic	Atonic	Atonic	Atonic	Atonic	Spastic	Periodic
Diagnosis	Chronic intestinal atony								

Chronic intestinal stasis, atonic type	7	14
Chronic intestinal stasis, spastic type	1	2
Chronic intestinal stasis, periodic	1	2
Intestinal stasis, total	9	18

50 cases studied

Three patients—6 per cent—had with the atony of the bowel an associated atony of the stomach

TABLE 21—INTESTINAL STASIS ASSOCIATED WITH GASTRIC ATONY

Number	1	2	3
Name	T P	T H	R L
Declaration, present	Negative	Negative	Negative
Declaration, past	Positive	Negative	Negative
History	Positive	Positive	Positive
Stomach empty	6 (plus) hrs	6 (plus) hrs	6 (plus) hrs
Greater curvature	Crest minus 2 in	Crest minus 2 in	Crest
Transverse colon	Low	Kinked	
Intestinal tract empty	72 hrs	120 hrs	72 hrs
Lumen of colon	Normal	Normal	Normal
Diagnosis	Chronic gastric and intestinal atony		
Chronic gastric and intestinal atony			3
50 cases studied			6 per cent

Nine patients—18 per cent—had with intestinal stasis, chronic inflammatory changes of the mucosa

TABLE 22—INTESTINAL STASIS ASSOCIATED WITH CHRONIC INFLAMMATION

Number	1	2	3	4	5	6	7	8	9
Name	M P	H O	L R	S J	K H	J A	C L	D G	B H
Declaration, present	Neg	Neg	Neg	Pos	Pos	Pos	Pos	Neg	Neg
Declaration, past	Neg	Neg	Pos	Pos	Pos	Pos	Pos	Pos	Pos
History	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
Stomach contents, lav ers				2	2			3	3
Mucus span				2 inch	2 inch			2 inch	2 inch
Free HCl				56	55			50	57
Stool mucus	Neg	Pos	Neg	Pos	Neg	Pos	Pos	Pos	Neg
Number of stools	2-6	2-5	0-5	0-6	0-6	0-1	1	1-6	2-3
Intestinal tract empty	48 hrs	72 hrs	48 hrs	96 hrs	72 hrs	48 hrs	48 hrs	48 hrs	96 hrs
Diagnosis	Chronic colitis with stasis				Chronic enterocolitis with stasis			Chronic gastro enterocolitis with stasis	
Chronic colitis with stasis							4	8 per cent	
Chronic enterocolitis with stasis							3	6 per cent	
Chronic gastro-enterocolitis with stasis							2	4 per cent	
Stasis associated with chronic inflammation—total							9	18 per cent	
50 cases studied									

Four patients—8 per cent—had evidences of either secondary or primary irritations, other than as classified in the foregoing

TABLE 23—SECONDARY GASTRO-INTESTINAL IRRITATION

Number	1	2	3	4
Name	B W	G J	C O	H L
Declaration, present	Positive	Negative	Positive	Negative
Declaration, past	Positive	Negative	Positive	Negative
History	Positive	Suggestive	Positive	Positive
Titration free HCl	59	67	71	
Stomach content after 50 minutes	100 c c 90	65 c c 21	60 c c 45	
Quotient	20	44	15	
Empty stomach	10 c c	25 c c	35 c c	
Mucus in stomach	Negative	Positive	Positive	
Occult blood in stomach	Negative	Negative	Negative	
Occult blood in stool	Negative	Negative 1 Positive 1	Negative 1 Positive 1	3 or 4 stools daily every week or two
Diagnosis and Remarks	(Two attacks jaundice with pain) History and physical examination makes gallstones most likely	Interstitial hepatitis, alcoholic, large liver 2 cm below costal arch, firm, food remained in cecum, transverse and descending colon empty	Pylorus sharply flexed on lesser curve, cap not distinct, 6 hrs no retention, peptic ulcer suggested	Meat in diet causes cramps and 3 or 4 stools a day, frequent attacks, suggestive of a pancreatic disturbance

Possible gallstones	1	2 per cent
Possible interstitial hepatitis	1	2 per cent
Possible pyloric ulcer	1	2 per cent
Possible pancreatic insufficiency	1	2 per cent
Secondary gastro intestinal irritation—total	4	8 per cent
50 cases studied		

Many of these twenty-five positive gastro-intestinal irritation cases, were of such high grade severity that it is remarkable that they did not come to our service on admission to the hospital. It is a common experience for patients with gastro-intestinal troubles to complain of palpitation, fast pulse, precordial pain, vasomotor disturbances, spots before the eyes, dyspnea on relatively slight exertion, dizziness or giddiness and complaints of general or local nervousness. Certainly no one would expect the receiving ward to make a careful differentiation of cases showing the N C A syndrome with pronounced symptoms of stomach and bowel troubles from stomach and bowel troubles with resulting or associated nervous manifestations. It is quite possible that these nervous patients, undergoing a new experience in entering the hospital, were having an accelerated pulse, and when the receiving officer asked them their complaints their attention was directed to their hearts, and they were assigned accordingly. On studying this very interesting series I was impressed not only with the fact that 50 per cent had gastro-intestinal irritations, but also with the large proportion showing other foci of irritation, such as diseased tonsils, numerous

carious teeth, many missing grinders, etc To all this internal scratching there was added the external irritation of having to leave home and go to camp, there to perform duties for which they had little or no liking What little nerve capital they had left after these more or less prolonged internal irritations was wiped out by the external irritation, by worry Their nerves were now without strength They were neurasthenic They could have carried the external irritation like other men if it had not been for the internal load

Removal of all possible foci of irritation surgically and dietetically places them in a condition favorable to reconstruction by graduated exercises To hasten reconstruction I think it is of considerable importance that these patients be taught practical points about nerve hygiene They should know how to discipline themselves, something they have never known or practiced, what self-discipline means, its importance, and just how it should be daily practiced, how to conserve their nerve capital which is gradually being acquired, and how to economize the pennies and nickles of nerve force They will thereby know more of practical value about themselves and become most interested in their own development

Size of the Heart—Following the plan of Meakins and Gunson, fifty patients were examined with the view of determining the size of the heart, and comparing with normal controls after Dietlen As in their report, weight was taken into consideration Comparison shows the average transverse diameter to be somewhat less in patients than in the controls What effect a rapid rate has on the heart size of these patients is not definite, since the men studied have not undergone such severe training We can at least be sure that the cases under consideration show no lesion of an organic nature

TABLE 24—COMPARING CARDIAC MEASUREMENTS IN PATIENTS AND CONTROLS

Number	Per Cent	Weight Pounds	Average Transverse Diameter by Percussion, in Patients, Cm	Average Trans verse Diameter by Roentgen- Ray, in Patients (72 Inches), Cm	Average Transverse Diameter in Controls,* Cm
5	10	110-120	12.1	11.8	11.9
4	8	121-130	12.4	12.6	12.9
10	20	131-140	12.5	12.0	12.9
9	18	141-150	13.5	12.5	12.9
6	12	151-160	14.4	13.1	13.4
11	22	161-170	13.6	12.9	14.3
4	8	171-180	13.4	12.8	14.3
1	2	181-190	14.5	13.5	14.4
Total 50	100		Average 13.3	Average 12.6	Average 13.4

* After Dietlen

Cardiac Configuration in Health and Disease—In comparing clinical and roentgen cardiac findings, a definite scale of measurement and configuration was desired. The large amount of clinical material at hand made possible the selection of cases with complicated and uncomplicated valvular lesions. Ten patients of each clinical type were collected and an average taken of the roentgen-ray findings. The configuration used in reading these plates ascribed the first right curve to the vena cava, the second right curve to the right auricle, the first left

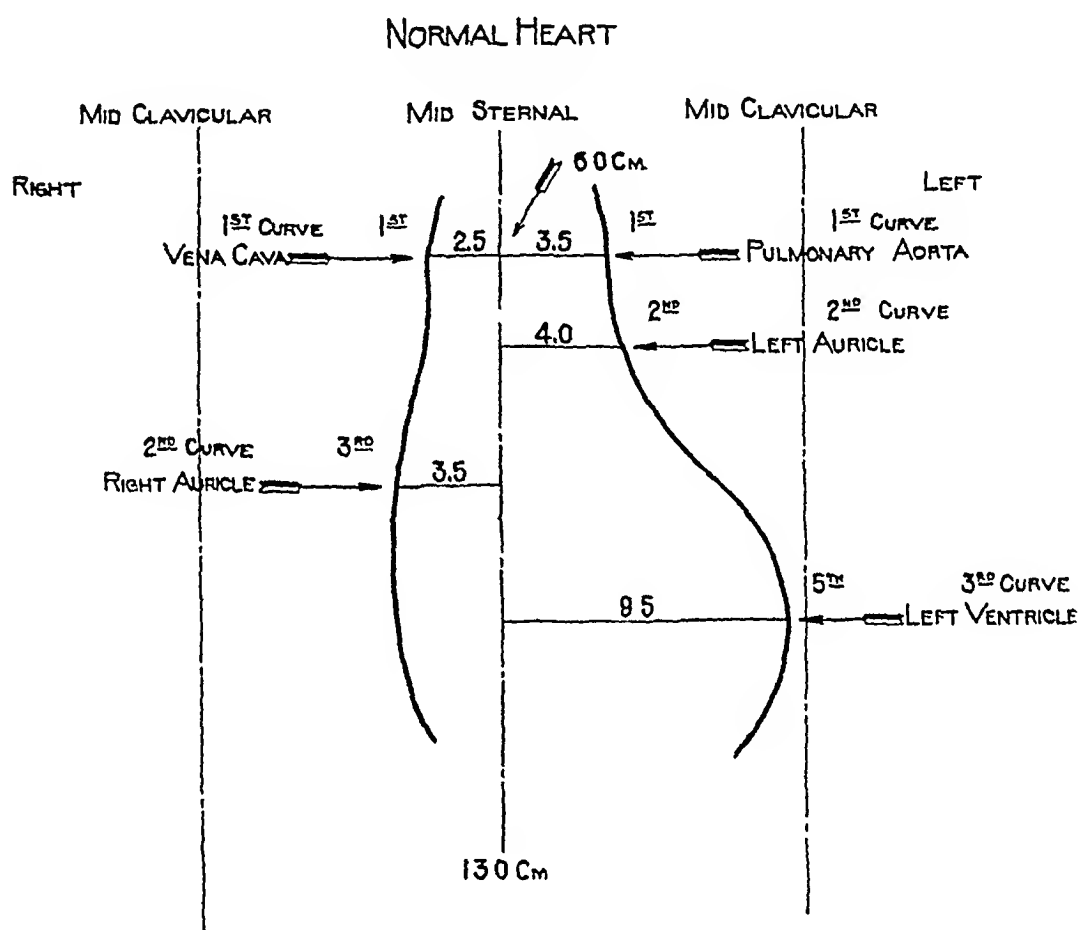


Chart 2—Plate distance, 72 inches. Scale in this and following charts, 0.5 cm = 1 cm.

to the pulmonary aorta, the second left to the left auricle and the third left to the left ventricle. In the accompanying configurations (Chart 2) the accentuated second left curve in pure mitral stenosis, the accentuated second and third left curves in combined mitral disease and the increased width of the base of the heart in aortic disease are typical. While measurements to be accurate should depend on the weight of the patient, the measurements in Chart 2 might be considered a fair average for a man of 150 pounds.

TABLE 25—COMPARING MEASUREMENTS IN HEALTH AND DISEASE,
FROM ROENTGEN CONFIGURATION

	Base, Cm	2nd Left, Cm	2nd Right, Cm	3rd Left, Cm	Trans verse, Cm
Normal heart, average 10 controls	60	40	35	95	130
Mitral insufficiency, average 10 patients	60	40	40	105	145
Mitral stenosis, average 10 patients	60	55	40	100	140
Combined mitral insufficiency and stenosis average 10 patients	60	85	45	110	155
Aortitis chronic with aortic dilatation, average 10 patients	80	80	55	100	155
Combined aortic and mitral disease, average 10 patients	90	80	70	130	200

MITRAL INSUFFICIENCY

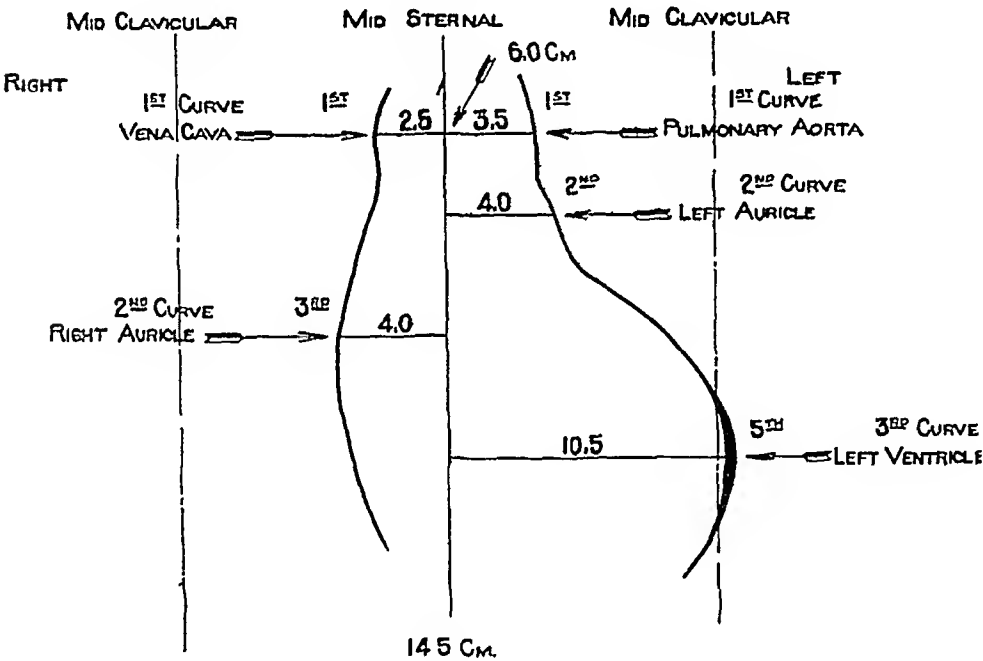


Chart 3

Comparison of Pulse Rate and Blood Pressure of Patients and Control—The cardiac rate in patients is somewhat variable, but on taking the average of one group and comparing it with that of others a definite conclusion can be reached. Patients in Group 1, or the first period of training, show a high variable pulse rate with a delayed return to normal. As the higher grade exercises are reached and tolerated, both the rate and response to exercise become more constant and approach more nearly that of the controls.

TABLE 26—REST RATE COMPARED BEFORE AND AFTER ONE HUNDRED HOPS ON LEFT FOOT

	Pulse		Blood Pressure		Return to Normal
	Before	After	Before	After	Minutes
Average 10 controls	76	120	{ 124 82 }	{ 136 84 }	1½
10 patients, Group 1	96	144	{ 132 84 }	{ 160 88 }	3½
10 patients, Group 3	90	132	{ 132 84 }	{ 160 86 }	3
10 patients, Group 5	84	128	{ 132 84 }	{ 156 84 }	2

Blood pressure readings are also inconstant and show no definite distinguishing feature. The systolic pressure is always somewhat higher in patients than in controls, while the diastolic shows very little difference.

Observations were made on ten men in the final group of training before and after taking a six-mile hike with light pack. This constituted a 90-minute march at a cadence of 120 steps a minute. The response to this test was not unlike that of the controls, three normal men. There was no dyspnea or evidence of distress. These men after a two months course of graduated exercises qualified for full military duty.

TABLE 27—REST RATE BEFORE AND AFTER SIX-MILE HIKE WITH LIGHT PACK

	Pulse		Respiration		Blood Pressure, Systolic		Blood Pressure, Diastolic		Return to Normal, Minutes
	Before	After	Before	After	Before	After	Before	After	
Average 5 controls	76	120	14	16	124	136	82	84	2½
Average 10 patients, Group 5	84	128	16	17	128	144	84	86	2

Effect of Tobacco and Alcohol—Of the fifty men under observation, 10 per cent used cigarets to excess (twenty and more daily), 20 per cent fifteen per day, 30 per cent moderately (average of ten cigarets per day), 28 per cent five per day, while 12 per cent did not use tobacco in any form. In this same group only 4 per cent admitted alcohol to excess, while 50 per cent used it moderately, 20 per cent in slight degree and 26 per cent had never used it in any form.

Pulse, respiration and blood pressure readings were made before and after smoking five cigarets in succession, the brand used being the

popular Camel. The reaction of ten controls was compared with that of ten men in Group 1, the first period of training, with ten men in Group 3, the midperiod of the course of exercises, and these with ten men of the graduating or final group. Observations on the reaction to exercise were made at the same time, in relation to the effect of smoking. In both patients and controls the pulse and respiratory rate rises after smoking. This, however, was more marked in patients than controls, but men having progressed to the highest grade of exercises reacted only slightly higher than the control, while those in the first class and in the midperiod of training showed a definite reaction. In all observations the reactions were temporary. Only three of the mid-group showed definite aggravation of symptoms, while the controls and the men boarded fit for full duty showed practically no untoward signs.

MITRAL STENOSIS

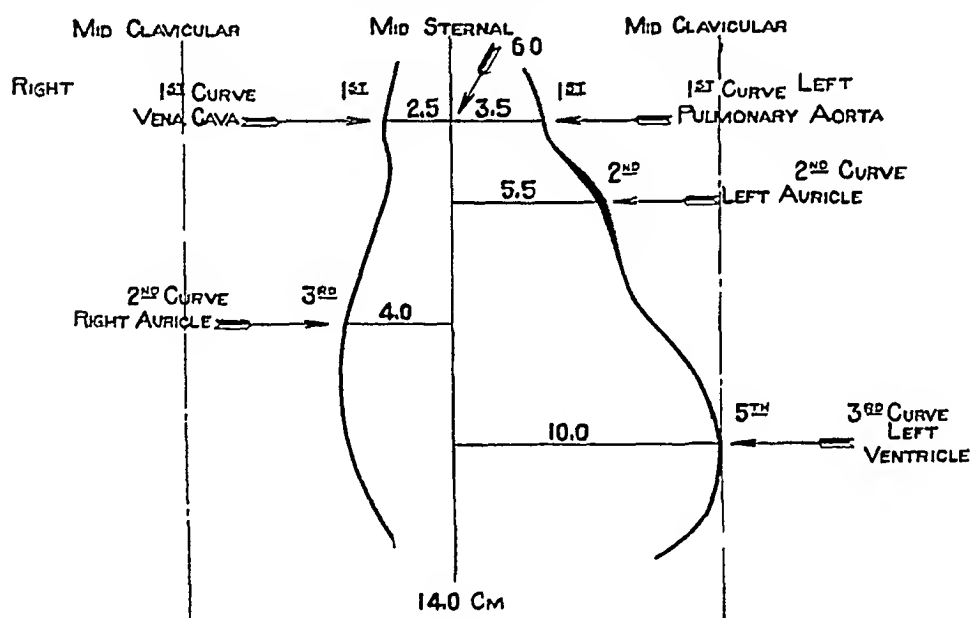


Chart 4

The 12 per cent of nonsmokers did not use alcohol. Their symptoms, however, when compared to those of the heavy smokers or excessive drinkers, were not in any way proportionally decreased. Thus, no conclusion can be drawn for a definite basis for production of symptoms. It is therefore evident from our observation that while alcohol and tobacco in excess aggravate the symptoms and signs of this syndrome, they are not a constant primary source of irritation.

TABLE 28—OBSERVATIONS ON SERIES OF FIFTY CASES UNDER STUDY

Average Consumption of Tobacco		Average Consumption of Alcohol	
Cigaretts per Day	Per Cent		Per Cent
20	10	Heavy	4
15	20	Moderate	50
10	30	Slight	20
5	28	Total abstainers	26
Nonsmokers	12		

Effect of Cigaret Smoking — The pulse, respiratory and blood pressure readings were made on ten healthy men before and after smoking five cigarettes in succession, and before and after exercise (100 hops on left foot) An average taken of these ten controls shows a normal response to exercise and a very slight reaction as an effect of smoking

TABLE 29—AVERAGE EFFECT OF SMOKING BEFORE AND AFTER EXERCISE IN TEN CONTROL CASES

	Pulse		Respiration		Blood Pressure, Systolic		Blood Pressure, Diastolic		Return to Normal, Minutes	
	Before	After	Before	After	Before	After	Before	After	Before	After
Before exercise	72	74	16	18	128	128	84	82	¼	¼
After exercise	108	110	20	22	160	160	88	86	1½	1½

Observations were also made on ten men reporting for the first class of graduated exercises This constitutes Group 1 in the schedule used The degree of reaction is greatest in this group when compared with that of the controls The increased rate is not a marked feature, but three of this group complained of definite breathlessness and a general sense of uneasiness

TABLE 30—AVERAGE PULSE, RESPIRATION AND BLOOD PRESSURE IN TEN CASES —GROUP 1—AFTER GRADUATED EXERCISES

	Pulse		Respiration		Blood Pressure, Systolic		Blood Pressure, Diastolic		Return to Normal, Minutes	
	Before	After	Before	After	Before	After	Before	After	Before	After
Before exercise	104	108	22	24	144	148	90	90	½	½
After exercise	152	160	24	26	164	180	92	96	3½	4

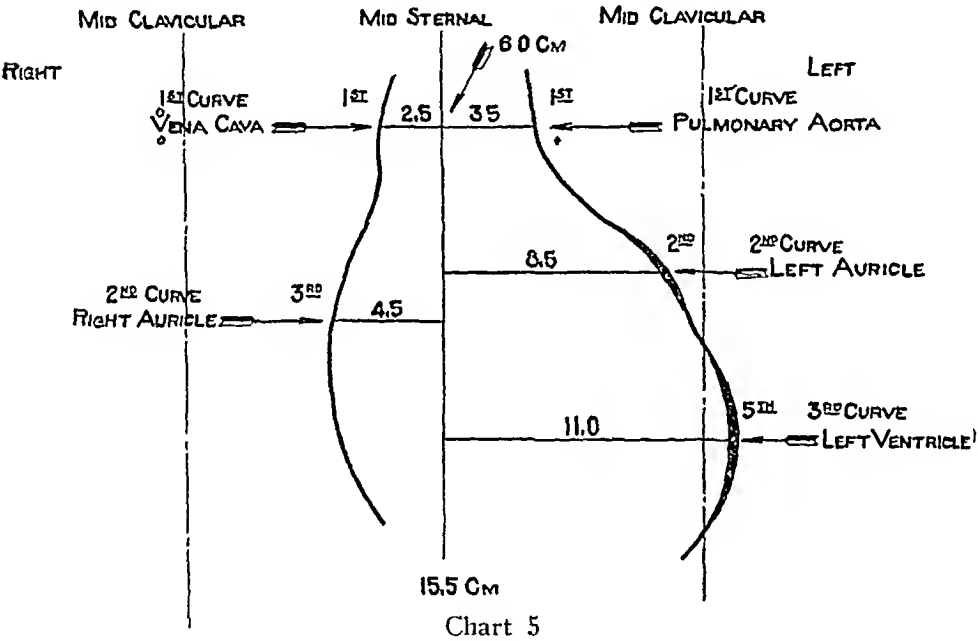
In Table 30 we find the resting rate high, with an exaggerated response to exercise There are many stimuli which influence the resting rate Smoking does this temporarily and to a mild degree The same effect is produced by a slight change of posture or emotion, so that it is rather difficult to arrive at a fixed average rate for this group

The average pulse, respiratory and blood pressure readings of ten patients in Group 3, the midperiod of training, are less variable and the reaction to smoking when compared with that of the controls is less marked

TABLE 31—AVERAGE PULSE, RESPIRATORY AND BLOOD PRESSURE READINGS IN TEN CASES—GROUP 3

	Pulse		Respiration		Blood Pressure, Systolic		Blood Pressure, Diastolic		Return to Normal, Minutes	
	Before	After	Before	After	Before	After	Before	After	Before	After
Before exercise	96	104	20	22	142	146	88	90	½	½
After exercise	124	132	24	26	156	160	92	92	3	3½

COMBINED MITRAL STENOSIS—INSUFFICIENCY



Group 5, consisting of men having progressed to the highest grade of exercises and who have tolerated them in conjunction with route marches without distress, compare most favorably with the ten controls. Here again the reaction to smoking is slight and the response to exercise only moderately exaggerated by external stimuli.

TABLE 32—AVERAGES IN TEN CASES—GROUP 5

	Pulse		Respiration		Blood Pressure, Systolic		Blood Pressure, Diastolic		Return to Normal, Minutes	
	Before	After	Before	After	Before	After	Before	After	Before	After
Before exercise	84	88	18	19	136	140	84	88	¼	¼
After exercise	118	122	22	24	144	148	86	88	2	2½

In summarizing, the tobacco reaction, pulse and respiratory and blood pressure readings were slightly higher in patients than controls. Patients in Group 5 compared most favorably with the controls, while those in Group 1 reacted in greater degree. Group 3, in accordance with their tolerance to exercise, reacted in moderate degree.

Effect of Atropin on the Heart Rate—Observations were made on ten patients compared with ten controls before and after the administration of $\frac{1}{30}$ grain atropin sulphate subcutaneously. The response to exercise (one hundred hops on the left foot) before and after atropinization was also noted. Twenty-five minutes were allowed to intervene for complete effect. Both patient and control showed the same results, namely, increased pulse rate approximately to the same degree following atropin. From this Lewis² concludes that the high cardiac rate in patients is not due to a reduction in vagal tone, but is more probably due to hyperirritability of some portion of the system including the accelerator reflex arc.

The patients presented for observation before administration of atropin showed marked dermatographia, cold, clammy, cyanotic hands and marked axillary sweating. After atropinization this picture was entirely changed, much to the surprise of the patients. Hands were dry, pink, hot and the dermatographia temporarily disappeared.

TABLE 33—EFFECT OF ATROPIN ON TEN PATIENTS

Atropin, 1/30 Gr	Rest Rate		After Exercise		Blood Pressure at Rest		Blood Pressure After Exercise	
	Before	After	Before	After	Before	After	Before	After
Average 10 controls	80	108	132	144	128	132	140	152
					80	84	80	86
Average 10 patients	88	118	128	158	132	136	146	160
					84	84	86	88

Thus, in our search for irritation it was determined that the mechanism by which increased rate of patients is arrived at is not altered vagal tone, but a hyperirritability of the system, including the accelerator reflex arc.

TABLE 34—FOCI OF IRRITATION

	No	Per Cent		No	Per Cent
General physical	14	28	Psychiatric	6	12
Thyroid	10	20	Neurologic	34	78
Ear	4	8	Gastrointestinal	25	50
Nose	16	32	Genito urinary	6	32
Sinuses	10	20	Syphilis	2	4
Throat	45	90	Alcohol	4	8
Teeth	18	36	Tobacco	5	10

2 Report by Cotton, Rapport, Lewis

Weights—During the entire period of training, weights were taken at six-day intervals. All men gained weight rapidly up through the group, including the highest grade of exercises. When route marches were taken in conjunction with the high grade exercises, without and with light and full pack, an average of one-half pound per man was lost from the admission weight.

TABLE 35—WEIGHT GAINED DURING PERIOD OF TRAINING

Pounds	No
Constant	5
1	1
2	1
3	1
4	2
5	2
7	2
Total	14
28 per cent gained weight	

TABLE 36—WEIGHT LOST DURING PERIOD OF TRAINING

Pounds	No
1	5
2	10
3	4
4	5
5	1
6	4
7	4
9	2
10	1
Total	36
72 per cent lost weight	

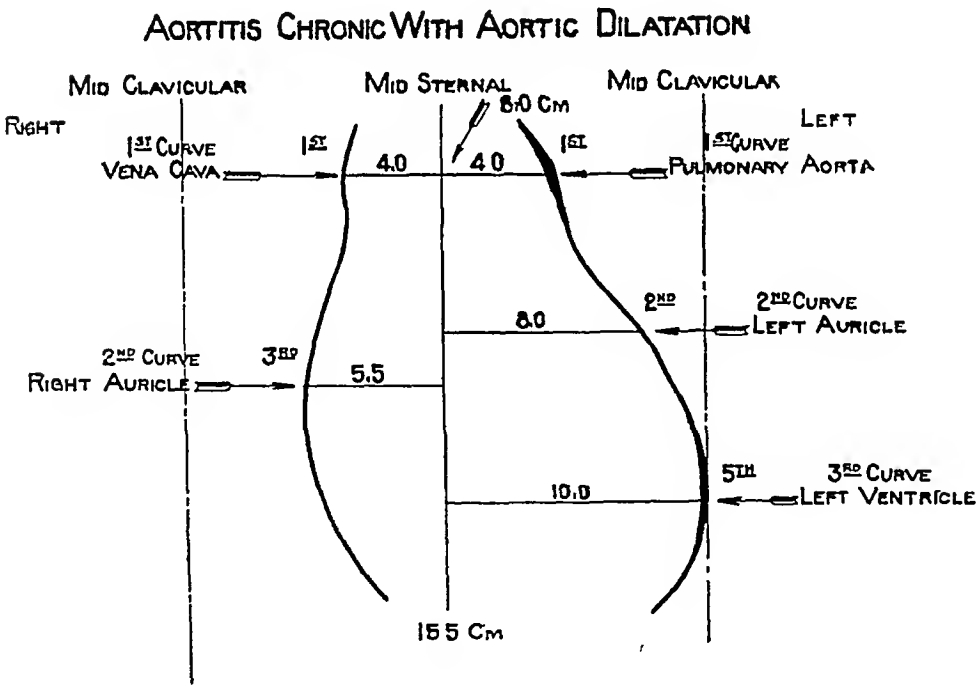


Chart 6

Final Disposition of Group Progress—In accordance with our policy of graduated exercises, the fifteen men who progressed to the highest grade exercises and carried them out without distress in conjunction with route marches of 6 miles, with full pack, were sent to

full and unrestricted military duty. These men had no complaints to offer and while there still remained some vasomotor instability, they were decidedly less sensitive to external stimuli, most of the internal foci having been removed, and they had learned that discipline and economy were necessary factors in the march to increased nerve capital. The twenty-five men who progressed more slowly, but toler-

COMBINED AORTIC — MITRAL DISEASE

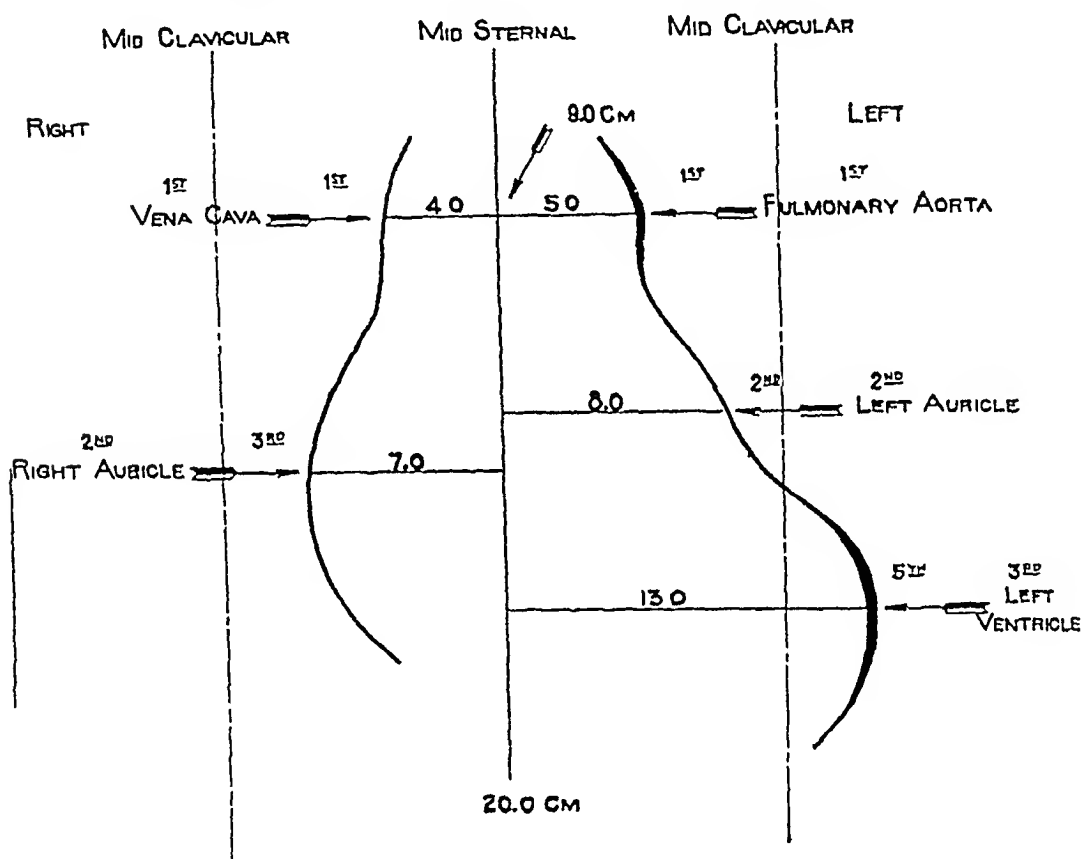


Chart 7

ated the exercises and route marches without undue distress, were sent to unrestricted domestic duty. An attempt was made to place these men in service according to their individual qualifications, in order that external stimuli be in some measure eliminated and that conservation and economy of nerve force be promulgated. The ten men showing continued symptoms on the highest grade exercises, but who progressed through all the stages, including route marches, were sent to limited domestic service. Of the group of fifty under study it was not considered necessary to discharge any man as permanently unfit.

TABLE 37—NEURO-CIRCULATORY ASTHENIA DATA OF INTENSIVE STUDY OF FIFTY CASES

No.	Age	Sex	Tool of Irritation												Weight		Occupation	Observation Time, Days	Group Progress and Disposition				
			Gen Physic	Cardiologic	Gastrointestinal	Psychiatric	Neurologic	Laryngeal	Dental	Roentgen Ray	Blood	Urine	Stool	Atomich Con tents	Gen ito nary	Was in Smoker				Prosthetic	To baccol	Alcohol	
1	26	8/12	+	-	-	-	+	+	-	-	-	-	-	-	-	-	+	-	165	162	Clerk	62	Lam domestic
2	26	8/12	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	159	155	Farmer	62	Lam domestic
3	32	7/12	-	+	-	-	+	+	-	-	-	-	-	+	-	-	-	-	129	129	Bookkeeper	62	Lam domestic
4	22	8/12	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	161	160	Farmer	62	Full duty
5	23	7/12	-	+	-	+	+	+	-	-	+	-	-	-	-	-	-	-	140	133	Farmer	62	Lam domestic
6	21	7/12	-	+	-	+	+	+	-	-	+	-	-	-	-	-	-	-	166	164	Farmer	62	Lam domestic
7	23	3/12	-	+	-	+	+	+	+	+	-	-	-	-	+	-	-	-	156	163	Engineer	62	Full domestic
8	22	3/12	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	149	174	Farmer	62	Full duty
9	30	7/12	-	+	-	+	-	+	-	-	-	-	-	+	-	-	-	-	158	149	Plumber	56	Full domestic
10	29	1/12	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	152	153	Constable	56	Full domestic
11	31	7/12	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	151	149	Printer	56	Full domestic
12	22	7/12	-	+	-	+	-	+	+	+	-	-	-	-	-	-	-	-	145	141	Farmer	56	Full duty
13	30	1/12	-	+	-	+	+	+	-	-	-	+	+	-	-	-	+	-	172	171	Laborer	56	Lam domestic
14	24	7/12	+	-	+	+	-	+	+	+	-	-	-	+	-	-	+	-	145	144	Clerk	56	Full domestic
15	30	2/12	-	-	+	-	-	+	+	-	-	+	+	+	+	-	-	-	168	175	Clerk	54	Full duty
16	28	1/12	+	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	180	174	Attorney	54	Full domestic
17	25	4/12	-	-	+	-	-	+	+	+	-	-	-	-	-	-	-	-	142	142	Optician	62	Full domestic
18	27	9/12	+	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	136	135	Mechanic	62	Full domestic
19	23	8/12	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	169	165	Clerk	62	Full duty
20	22	9/12	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	115	109	Farmer	62	Full domestic
21	24	2/12	+	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	179	170	Fitter	62	Full domestic
22	26	1/12	-	-	+	-	-	-	+	-	-	-	-	-	-	-	-	-	122	120	Mechanic	62	Full domestic
23	23	2/12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	159	160	Architect	34	Lam domestic

TABLE 38—DISPOSITION OF MEN IN GROUPS STUDIED

	No	Per Cent
Unrestricted military duty	15	30
Group progress, good		
Unrestricted domestic duty	25	50
Group progress, good, highest grade exercises tolerated less perfectly		
Ordnance	1	
Electrician	1	
Shoe repair	1	
Drill instructors	3	
Typists	4	
Teamsters	4	
Carpenters	3	
Motor truck repair	3	
Pipe fitter and plumbers	1	
Cook	1	
Printer	1	
Laborers	2	
Limited domestic service	10	20
Group progress, fair, highest grade exercises only fairly well tolerated		
Artist illustrators	2	
Clerks	3	
Medical detachment	1	
Orderlies	2	
Teamsters	2	
Total	50	100

In our early experience with this group all were deemed unfit for military duty, and under former conditions had been withdrawn from their organizations and sent to the Depot Brigade, pending discharge from the National Army. We now return fifty salvaged men to duty, fifteen to unrestricted military duty, twenty-five to unrestricted domestic duty, ten to limited domestic duty.

Our object has been not only to study these men presenting this syndrome from an etiologic and therapeutic point of view, but to prevent any questionable case going overseas, there to become a burden, before subjection to a rigid investigation and graduated method of sorting.

Observation Time—Fifty per cent of this group had been in service eight months, 25 per cent three months, 25 per cent one month. Under the present system of graduated training and discipline, observation time averaged seven weeks from time of admission to discharge to duty, a saving of six months. This is not only a great difference in time and expense to the government, but to the recruit on whose early training so much depends.

THE EXCRETION OF CREATIN, CREATININ, AND URIC ACID IN ACUTE FEBRILE CONDITIONS⁺

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The excretion of creatin, creatinin and uric acid in the urine during the course of acute infectious fevers has been studied by Cathcart,¹ Van Hoogenhuyze and Verploegh,² af Klercher,³ Kocher,⁴ Shaffer,⁵ Ewing and Wolf,⁶ Shaffer and Coleman,⁷ and others. Their results agree as regards the finding of creatinuria, and an increased output of creatinin and of uric acid. The diets used by most investigators were at times in the course of the experiments of insufficient caloric value and not particularly rich in carbohydrates. Shaffer and Coleman have investigated the effects of high caloric diets, rich in carbohydrates, on the protein metabolism of patients with typhoid fever. They found that these diets retarded or prevented the loss of body protein in their cases. For this reason it was considered important to study the excretion of certain of the products of protein metabolism in the different varieties of acute febrile conditions at a time when the affected patients were receiving a "Shaffer-Coleman diet." The products chosen were creatin, creatinin and uric acid because of the accuracy with which their endogenous amounts can be determined.

EXPERIMENTAL PROCEDURE

Patients were given the diet proposed by Shaffer and Coleman, except that no purin- or nuclein-containing foods were fed. The diet contained approximately from 3,000 to 4,000 calories of protein, fat and carbohydrate in each day's feeding. Urine specimens were preserved on ice under toluol. Uric acid, creatin, and creatinin were determined by the methods of Folin.⁸ In

* Submitted for publication July 17, 1918

1 Cathcart. Uric Acid Output and Heat Production, Proc Roy Soc, London, 1907, **79**, 13

2 Van Hoogenhuyze, C J C, and Verploegh, H. Weitere Beobachtungen über die Kreatininausscheidungen beim Menschen, Ztschr f physiol Chem, 1908, **57**, 162

3 af Klercher, KJ, O. Ueber Ausscheidung von Kreatin und Kreatinin in fieberhaften Krankheiten, Ztschr f klin Med, 1909, **68**, 22

4 Kocher, R A. Ueber die Grosse des Eiweisszerfalls bei Fieber und bei Arbeitsleistung, Deutsch Arch klin Med, 1914, **115**, 82

5 Shaffer, P. The Excretion of Kreatinin and Kreatin in Health and Disease, Am Jour Physiol, 1908-1909, **23**, 1

6 Ewing, J, and Wolf, C G L. The Clinical Significance of the Urinary Nitrogen, THE ARCHIVES INT MED, 1909, **4**, 330

7 Shaffer, P A, and Coleman, W. Protein Metabolism in Typhoid Fever, THE ARCHIVES INT MED, 1909, **4**, 538

8 Folin, O. On the Determination of Creatinin and Creatin in Urine, Jour Biol Chem, 1914, **17**, 469. A Laboratory Manual of Biological Chemistry, New York, 1916, p 93

determining uric acid the "uric acid reagent" was used instead of the "uric acid-phenol reagent" Otherwise the method was employed as given in Folin's manual Phosphorus was quantitated by the uranium acetate titration method All temperatures recorded in the appended table are rectal temperatures A total of eight febrile conditions has been studied, comprising six cases of typhoid fever, four cases of lobar pneumonia, one case of streptococcic bronchopneumonia, two cases of tuberculous bronchopneumonia, two cases of pulmonary tuberculosis, one of which was complicated by hemopneumothorax, one case of subacute rheumatic fever, and two cases with fever of unknown cause

The Relation of Creatinuria to Fever—Creatinuria was present throughout the febrile periods in two cases (2, 3, see table) In another case (1) the output of creatin ceased nine days prior to the disappearance of the pyrexia In one case creatinuria was present during one period of fever and absent throughout the course of a second febrile period in this patient (5) Creatinuria was either completely absent or present in small amount in five febrile cases (5, 6, 7, 8, 9) In three of these fever was present over periods of observation of from one to four weeks Two cases were febrile but a short time One of these showed no creatinuria, and the other a small amount on two occasions Another case (12) had very slight creatinuria during two periods of high fever Postfebrile creatinuria persisted for seven to ten days in two cases (13, 14), and in three others (2, 5, 12) it was present for a few days

These findings show that there was no constant relation between the presence of pyrexia and creatinuria

The Relation of Creatinuria to Loss in Body Weight—In seven cases loss in body weight was accompanied by creatinuria (1, 2, 3, 4, 10, 13, 14) In three of these (3, 13, 14) creatin did not disappear from the urine with the cessation of the loss in body weight In one case (3) creatinuria was present during weeks in which there was very little or no loss in weight, as well as during the time when rapid loss occurred One patient (12) had slight creatinuria during a period of loss in weight and again during a period when there was a gain in weight Two patients showed only an occasional slight creatinuria during periods of moderately rapid loss in body weight

These findings show that the presence of creatinuria, although usually occurring coincidently with loss in body weight, is not definitely related to either the rapidity or the amount of weight lost

The Relation of Creatinuria to the Increase in the Excretion of Creatinin and of Uric Acid—Creatinuria was associated with disturbances in the excretion of both creatinin and uric acid in four cases (2, 3, 14, 15) In two cases (4, 13) there was a considerable amount of creatin excreted while the output of creatinin remained normal In all but one case in which creatinuria occurred there was also an increased elimination of uric acid In this case (12) there was a slight creatinuria, which was not accompanied by an abnormal crea-

tinin or uric acid output. These findings show that during periods of pyrexia creatinuria may occur unaccompanied by disturbances in the excretion of uric acid and of creatinin.

Creatinin—In most cases the amounts of creatinin excreted were increased during the periods of pyrexia. This increase was often present only at irregular intervals. In one case (9) the disturbance in the output of creatinin was as great during the afebrile as during the febrile period. In two cases (11, 12) no increase in the amounts of creatinin excreted occurred in spite of the presence of high fever. A disturbance in the excretion of creatinin was found in one case (9) without associated anomalies in the elimination of uric acid or of creatin. These findings demonstrate that in certain of the febrile diseases, (a) disturbances in the excretion of creatinin are not necessarily associated with an increase of the body temperature, and (b) that such disturbances may occur independently of anomalies in the excretion of uric acid and creatin. An increase in the output of creatinin was not related to loss of body weight in all cases.

Uric Acid—In all but two cases uric acid was excreted in abnormally large amounts during the periods of pyrexia (9, 12). A post-critical increase in the amounts of uric acid eliminated persisted over periods of from five to nine days in five cases (1, 14, 16, 17, 18). Creatinuria was present in three of these cases, in one of which an increased creatinin output, also, occurred. No examination for creatin in the urine was made in the other two cases. In one case (18) an increase in the excretion of phosphorus accompanied the enlarged output of uric acid. These findings show that an increase in the output of uric acid during the course of the acute infectious diseases is not wholly dependent on the presence of pyrexia. In this connection it is interesting to note that Mandel⁹ found a decrease in the output of uric acid in three cases of "aseptic fever."

In six cases (1, 2, 9, 12, 14, 17) anomalies in the excretion of one of the three substances studied occurred during the second or the third week of convalescence. No definite relationship was found between the severity of the symptoms manifested by the patients and the amounts of creatin, of creatinin and of uric acid found in the urine.

SUMMARY AND DISCUSSION

Endogenous creatinin and creatin are considered as products of the metabolism of muscular tissue. An increase in the amount of creatinin excreted may be regarded as evidence of an increase of katabolism in the muscles, or possibly of an actual destruction of that tissue. The significance of creatinuria is not definitely known. In

⁹ Mandel, A. R. Xanthin as a Cause of Fever and Its Neutralization by Salicylates, *Am Jour Physiol*, 1907-1908, **20**, 439.

view of the work of Folin¹⁰ and of Denis¹¹ the creatinuria observed in the experiments here reported can readily be explained as the result of an over-production of creatin "If so much creatin is manufactured that the muscles become supersaturated, creatin is excreted by way of the kidneys"¹¹ On the other hand, there are some observers¹² who support the view that creatinuria is an expression of an incomplete oxidation of creatin in the body Acidosis may play a rôle in the production of creatinuria¹³ However, no studies concerning the presence of acidosis were made during the course of the experiments here reported The origin of endogenous uric acid from the nucleoprotein of the body tissues is fairly well established It is impossible to ascertain the exact source of the nucleoprotein from which the excess of uric acid, found during the course of these experiments, was derived The increase in the elimination of uric acid was no greater in those diseases accompanied by leukocytosis than in those in which this did not occur This finding shows that the disintegration of leukocytes played a minor rôle in its production Nevertheless, it is fair to assume that a certain amount of the excess of the uric acid eliminated during the stage of resolution in pneumonia was derived from the absorption of the pulmonary inflammatory exudate However, a postcritical increase in the output of uric acid occurred in other disease conditions in which no such exudate was present Also, it was not found in two of the cases of lobar pneumonia studied, but in these cases the areas of pulmonary consolidation were small A postcritical increase in the excretion of uric acid was accompanied, in certain cases, by creatinuria and an excessive output of creatinin The latter two phenomena would not result from the breaking down of cellular inflammatory

10 Folin, O., and Denis, W. Protein Metabolism from the Standpoint of Blood and Tissue Analysis VII An Interpretation of Creatin and Creatinin in Relation to Animal Metabolism, *Jour Biol Chem*, 1914, **17**, 493

11 Denis, W. The Influence of the Protein Intake on the Excretion of Creatin in Man, *Jour Biol Chem*, 1917, **30**, 47 Denis, W., and Kramer, J. G. The Influence of Protein Intake on Creatin Excretion in Children, *Jour Biol Chem*, 1917, **30**, 189 Denis, W., and Minot, A. S. The Production of Creatinuria in Normal Adults, *Jour Biol Chem*, 1917, **31**, 561

12 Mendel, L. B. and Rose, W. C. Experimental Studies on Creatin and Creatinin I The Role of the Carbohydrate in Creatin-Creatinin Metabolism, *Jour Biol Chem*, 1911-1912, **10**, 213 Benedict, S. R., and Osterberg, E. Studies in Creatin and Creatinin Metabolism III On the Origin of Urinary Creatin, *Jour Biol Chem*, 1914, **18**, 195 Rose, W. C. Experimental Studies on Creatin and Creatinin V Protein Feeding and Creatin Elimination in Pancreatic Diabetes, *Jour Biol Chem*, 1916, **26**, 331 Rose, Mary S. Creatinuria in Women *Jour Biol Chem*, 1917, **32**, 1 Janney, N. W., Goodhart, S. P., and Isaacson, V. I. The Endocrine Origin of Muscular Dystrophy, *THE ARCHIVES INT MED*, 1918, **21**, 188

13 Underhill, F. P. Studies in Creatin Metabolism I Possible Interrelation Between Acidosis and Creatin Elimination, *Jour Biol Chem*, 1916, **27**, 127 Underhill, F. P., and Baumann, E. J. Studies in Creatin Metabolism IV The Relationship of Creatinuria to Carbohydrate Metabolism and Acidosis, *Jour Biol Chem*, 1916, **27**, 151

exudates They would result from a disturbance in muscular metabolism These evidences of postcritical disturbances in metabolism warrant the conclusion that the excess of uric acid excreted during this period was, in part, derived from the nucleoprotein of the body tissues and not wholly from the absorption of cellular inflammatory exudates

It was found that creatinuria, or an increased output of creatinin, or of uric acid may each occur singly or in any combination with each other This indicates that there is not an inseparable relationship between the metabolisms of these three substances

The inconstant occurrence of creatinuria, and, to a less extent, of an increase in the outputs of creatinin and of uric acid, in the presence of pyrexia may, in part, be explained by the sparing action of carbohydrate on the body protein The latter is well illustrated in the work of Shaffer and Coleman, and of Graham and Poulton¹⁴ The former investigators did their work on typhoid fever patients, and the latter on normal men in whom pyrexia was induced by exposure to unusually high temperatures From their results they concluded that the loss of body protein could be retarded or prevented during periods of pyrexia by the use of high caloric diets rich in carbohydrates In spite of such diets, and in spite of the absence of weight loss, disturbances in the excretion of creatin, of creatinin and of uric acid were not always absent in the experiments here reported It therefore seems probable that these disturbances were, in part at least, an expression of the effect of toxins This view is supported by the studies of Dubois and his co-workers¹⁵ The findings of these investigators indicate that in typhoid fever and malaria a toxic destruction of protein occurs Whether toxins act by increasing katabolism or by actual disintegration of body tissue is not definitely known The disintegration of body tissue would seem to be unusual in patients receiving high caloric diets and who are not losing weight, either during periods of pyrexia or, especially, during convalescence Nevertheless, it must be borne in mind that certain pathologic structural changes occur in the different body tissues in the presence of continued pyrexia The relation of these degenerative changes to the presence of creatinuria, and to an increase in the production of creatinin and uric acid are unknown If such pathologic changes were an important factor in the production of these phenomena, constant relations in the excretion of creatin, of creatinin, and of uric acid would be expected, under comparable experimental conditions Since the relations in the excretions of these sub-

14 Graham, G, and Poulton, E P The Influence of High Temperature on Protein Metabolism with Reference to Fever, *Quart Jour Med*, 1912, **6**, 82 and 124

15 Coleman, W, and Dubois, E F Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, *THE ARCHIVES INT MED*, 1915, **15**, 887 Barr, D P, and Dubois, E F The Metabolism in Malarial Fever, *THE ARCHIVES INT MED*, 1918, **21**, 627

stances were found to be variable, the degenerative changes occurring in the tissues during pyrexia probably play but a minor rôle in the production of creatinuria, or of an increase in the excretion of uric acid and of creatinin. Therefore, the findings in the experiments here reported support the view that the toxins of the acute infections and of tuberculosis cause an increase in katabolism.

The presence of postcritical creatinuria, of an increased output of creatinin, and of uric acid show that disturbances of metabolism may extend into convalescence. This has been pointed out by Shaffer and Coleman. The occasional recurrence of abnormalities in the excretion of these three substances, after convalescence is well established, suggests that either disturbances in their metabolism are persisting, or that they are easily reproduced.

No creatin was excreted during the course of a very mild case of pneumonia and in certain febrile conditions of short duration which were studied. In severer types of pneumonia, and in long continued febrile states creatinuria was invariably present except in tuberculosis. The apparent rarity of creatinuria in the latter disease may prove, on further study, to be of value in the differential diagnosis of that disease.

The diet used in these experiments was well tolerated. The amounts of creatinin, frequently of creatin, and less often of uric acid, which were excreted were smaller than was to be expected from a comparison of the findings here reported with those of other investigators who did not feed a high caloric diet rich in carbohydrate. Shaffer and Coleman have shown that by the use of such a diet the amount of creatinuria in typhoid patients could be markedly diminished. Loss of weight was slight or completely absent under conditions in which it would naturally be expected. In certain cases an initial loss in weight occurred during the first week in the hospital. It then stopped, although there was no cessation in the symptoms of the disease. These findings show that the "Shaffer-Coleman" diet is a rational adjunct to the treatment of acute febrile diseases.

In selecting patients for study, those without evidences of nephritis were selected as far as this was possible. Certain findings common to nephritis are of frequent occurrence in the presence of fever. The results obtained in those cases in which such findings persisted into convalescence were rejected. The prevention of the loss of a certain number of specimens is very difficult when (1) urine is collected over long periods of time, (2) from acutely ill patients, (3) in the hospital wards. This does not vitiate the results, since the interpretation of findings deals only with abnormally large amounts of the substances studied. For purposes of comparison it is of importance to know the true endogenous level of the substances determined. This can be accomplished by following these determinations well into convalescence, which has been done wherever possible.

CONCLUSIONS

1 Disturbances in the excretion of creatin, creatinin and uric acid during the febrile period of the acute infectious diseases are, largely, an expression of the effect of toxins on metabolism. These disturbances may continue into the period of convalescence.

2 It has been found that the increased excretion of uric acid almost invariably accompanied acute febrile states. It was usually associated either with creatinuria, or with disturbances in the output of creatinin. At times all three phenomena were present.

3 The experimental findings indicate that the loss of uric acid, creatin and creatinin by the body, during acute febrile conditions, is retarded by a high caloric diet rich in carbohydrates.

SYNOPSIS OF CASE REPORTS

CASE 1—J J, white, man, aged 34, was admitted to St Luke's Hospital, Nov 12, 1917, and discharged recovered, Dec 19, 1917.

Diagnosis Typhoid fever

The past medical history was unimportant. The present illness began three weeks before admission to the hospital, with headache, malaise, lassitude, weakness, epistaxis and diarrhea. These symptoms increased in severity, and two weeks before admission the patient was confined to bed. Nov 12, 1917, the physical examination was essentially negative. Blood examination, Nov 12, 1917 hemoglobin, 80 per cent (Sahl), white cells, 3,440 per c mm, differential count, polynuclear leukocytes, 75 per cent, small lymphocytes, 20 per cent, large mononuclears, 5 per cent. The Widal reaction was positive in a dilution of 1:80. Blood culture was sterile. The Wassermann reaction was negative. Weekly examinations of the urine were negative except for the finding of a trace of albumin on one occasion. Phenolsulphonephthalein excretion was 40 per cent in two hours. Sputum and stool examinations were negative. The course of the disease was uneventful. The patient did not manifest the symptoms of severe toxemia.

CASE 2—J M, white, man, aged 35, was admitted to St Luke's Hospital, Nov 26, 1917, and discharged recovered, Jan 8, 1918.

Diagnosis Typhoid fever

The previous medical history was unimportant. The present illness began seventeen days prior to entering the hospital, with nausea, vomiting and diarrhea. The patient was not confined to bed until after admission to the hospital. The physical examination on November 26, was essentially negative. Blood examination, November 26 hemoglobin, 90 per cent (Sahl), white cells, 3,360 per c mm, differential count, polynuclear leukocytes 74 per cent, small lymphocytes 16 per cent, large mononuclears 10 per cent. The Widal reaction was positive in a dilution of 1:80. The blood culture showed the typhoid bacillus. The Wassermann reaction was negative. Examinations of the urine showed an occasional trace of albumin during the febrile period but no other pathologic elements. Phenolsulphonephthalein excretion was 60 per cent in two hours. Examinations of the sputum and feces were negative.

The course of the disease was uneventful. At times a mild delirium was present.

CASE 3—L M, white, man, aged 20, was admitted to St Luke's Hospital, Nov 29, 1917, and discharged recovered, Jan 16, 1918.

Diagnosis Typhoid fever

The past medical history was unimportant. The present illness began two weeks prior to admission to the hospital, with malaise, lassitude, anorexia, nausea, weakness, and slight epistaxis. November 21 the patient was first confined to bed. November 30 the physical examination was essentially negative. Blood examination, November 29: hemoglobin, 80 per cent (Sahli), white cells, 5,200 per cmm, differential count, polynuclears 70 per cent, small lymphocytes 24 per cent, large mononuclears 5 per cent, eosinophils 1 per cent. The Widal reaction was positive in a dilution of 1:80 and the blood culture showed typhoid bacilli. The Wassermann reaction was negative. Urine examinations were negative, except for a trace of albumin on one occasion. Phenolsulphonephthalein excretion was 60 per cent in two hours. Examination of the feces was negative.

The only striking feature during the course of the disease was that the hemoglobin fell from 80 per cent on November 28, to 50 per cent by December 5, after which date it gradually again increased.

CASE 4—A F, white, man, aged 47, was admitted to St. Luke's Hospital, Nov. 22, 1917, and discharged recovered, Dec. 24, 1917.

Diagnosis: Rheumatic fever (subacute).

No history was obtainable since the patient spoke only Italian. His physician sent the patient to the hospital with the diagnosis of rheumatic fever. On admission to the hospital the patient complained of pain in the right popliteal space and muscles of the thigh on motion of the leg. Slight pain in the deltoid muscles was caused by motion of the arms. There was some stiffness of the fingers and slight pain on motion in the metacarpophalangeal joints. The skin over the knuckle joints was somewhat reddened. The backs of the hands appeared to be swollen but did not pit on pressure. Otherwise, physical examination was negative. Blood examination, Nov. 22, 1917: hemoglobin, 60 per cent (Sahli), white cells, 25,680 per cmm. Differential count: polynuclear leukocytes 90 per cent, small lymphocytes 5 per cent, large mononuclears 5 per cent. Blood culture was negative. The Wassermann reaction was positive on two occasions. Urine examinations were negative. Phenolsulphonephthalein excretion was 60 per cent in two hours.

The meager objective symptoms of arthritis disappeared within a week. Up to within a few days of the subsidence of the fever the patient had occasionally painful joints, but only on motion. The leukocytosis disappeared shortly before the return of the temperature to normal.

CASE 5—J M, white, man, aged 25, was admitted to St. Luke's Hospital, Nov. 27, 1917, and discharged recovered, Jan. 1, 1918.

Diagnosis: Bronchopneumonia (streptococcal).

The patient spoke only Greek and no history was obtainable. Physical examination, November 28, elicited dullness in the lower right axilla and at the base of the right lung posteriorly. Over these areas breath sounds were almost inaudible and there were numerous fine crackling râles and a pleural friction rub. Over the upper portion of the right chest there were a small number of medium sized crackling râles. Roentgenographic studies showed scattered areas of consolidation throughout the right lung. Blood examination, November 29: hemoglobin, 75 per cent (Sahli), white cells, 10,000 per cmm, differential count, polynuclear leukocytes 74 per cent, small lymphocytes 25 per cent, large mononuclears 1 per cent. December 8, white cells, 9,720 per cmm, December 19, white cells 24,800 per cmm. The blood culture on November 28 showed a growth of streptococci, and on December 12, it was negative. During the periods of fever the urine examinations showed a trace of albumin to be present. Phenolsulphonephthalein excretion was 60 per cent in two hours. Sputum examinations showed no acid fast bacilli. The fever fell by crisis two days after admission of the patient to the hospital. The temperature remained normal for two weeks and then a second febrile period began. The areas of dullness in the chest and the roentgenographic findings

persisted until a short time before the patient was discharged Throughout the course of the disease symptoms of severe toxemia were not manifested

CASE 6—M M, white, man, aged 19, was admitted to St Luke's Hospital, Nov 10, 1917, and discharged improved, Nov 23, 1917

Diagnosis Pulmonary tuberculosis

The past medical history was unimportant The present illness had begun nine days prior to admission to the hospital, with headache, backache, anorexia, and a nonproductive cough Physical examination, November 11, elicited the signs usual of consolidation in the apex of the left axilla Roentgenograms showed a well defined area of consolidation in the upper lobe of the left lung and smaller areas scattered throughout the remainder of the lung Blood examination, November 11 hemoglobin, 85 per cent (Sahli), white cells, 6,960 per cmm, differential count, polynuclear leukocytes 70 per cent, small lymphocytes 25 per cent, large mononuclears 5 per cent The Widal reaction and the blood culture were negative The Wassermann reaction was positive Sputum examinations showed no acid fast bacilli Examinations of the urine and feces were negative Phenolsulphonephthalein excretion was 60 per cent in two hours

The patient had only an occasional slight cough during his stay in the hospital The fever gradually decreased There were no complications

CASE 7—E P, white man, aged 27, was admitted to St Luke's Hospital, Nov 18, 1917, and discharged improved, Dec 24, 1917

Diagnosis Hemopneumothorax, pulmonary tuberculosis

The past medical history was unimportant The history of the present illness was indefinite, since the patient had been on an alcoholic spree prior to admission to the hospital On physical examination, November 19, there were found signs characteristic of pleurisy with effusion involving the entire left chest To these signs were added a distinct "coin sound," especially audible over the lower half of the left chest On thoracentesis air and several hundred cubic centimeters of blood were aspirated from the left pleural cavity Blood examination, November 19 hemoglobin, 70 per cent, white cells, 26,720 per cmm, differential count, polynuclear leukocytes 72 per cent, small lymphocytes 26 per cent, large mononuclears 2 per cent The Wassermann reaction was negative The examinations of the urine were negative except for the occasional finding of a trace of albumin and a hyaline cast Phenolsulphonephthalein excretion was 60 per cent in two hours The sputum examinations showed no acid fast bacilli

The patient manifested no signs of severe toxemia throughout his stay in the hospital The physical findings did not change

CASE 8—V I, white man, aged 43, was admitted to St Luke's Hospital Nov 29, 1917, and discharged recovered Dec 19, 1917

Diagnosis Fever of unknown cause

No history obtainable, the patient did not speak English

Physical examination, November 30, was essentially negative Blood examination, December 1 hemoglobin, 75 per cent (Sahli), white cells, 2,520 per cmm, differential count, polynuclear leukocytes, 60 per cent, small lymphocytes, 30 per cent, large mononuclears, 10 per cent The Widal reaction was negative Examinations of the feces, sputum and urine were negative

The course of the patient's disease was uneventful There were no manifestations of severe toxemia

CASE 9—W C, white, man, aged 27, was admitted to St Luke's Hospital Dec 3, 1917, and discharged recovered Jan 5, 1918

Diagnosis Lobar pneumonia (type not determined)

The past medical history was unimportant The present illness began two days before admission to the hospital, with a chill and pleuritic pain in the left side of the chest On physical examination, December 14, a small area

of pulmonary consolidation was found in the region of the angle of the scapula in the left back. The roentgenogram showed a small area of consolidation to be present in this region. Blood examination, December 14: hemoglobin, 80 per cent (Sahli), white cells, 19,000 per cmm, differential count, polynuclear leukocytes, 78 per cent, small lymphocytes, 14 per cent, large mononuclears, 8 per cent. The sputum was mucopurulent and blood tinged. No acid fast bacilli were found. The examinations of the feces and urine were negative. Phenolsulphonephthalein excretion was 60 per cent in two hours.

The fever fell by lysis. The area of consolidation disappeared after twelve days' stay in the hospital.

CASE 10—A C, white, man, aged 28, was admitted to St Luke's Hospital Jan 9, 1918.

Diagnosis: Tuberculous bronchopneumonia.

The past medical history was unimportant. The present illness began three weeks prior to admission to the hospital, with anorexia, frequent vomiting and much coughing, with a large amount of mucopurulent sputum. On physical examination, January 10, signs of pulmonary consolidation were found at the angle of the scapula, the apex of the axilla and the anterior portion of the right chest. Medium and fine crackling râles were audible throughout both lungs. Blood examination, January 1: hemoglobin, 70 per cent (Sahli), white cells, 16,480 per cmm, differential count, polynuclear leukocytes, 70 per cent, lymphocytes, 26 per cent, large mononuclears, 4 per cent. Blood culture was negative. The Wassermann reaction was negative. The urine contained a faint trace of albumin, but no other pathologic elements. The sputum contained acid-fast bacilli.

The patient was still under observation January 24. Other than the cessation in the loss in weight his condition remained the same during observation in the hospital.

CASE 11—S J, white, man, aged 50, was admitted to St Luke's Hospital Dec 23, 1917.

Diagnosis: Tuberculous bronchopneumonia.

The past medical history was unimportant. The present illness began two months prior to admission to the hospital with weakness and anorexia. Three days before admission he was seized suddenly with pleuritic chest pain, a productive cough and vomiting. Physical examination, December 24, revealed signs of pulmonary consolidation over the entire front of the right side of the chest. Numerous medium and fine crackling râles were present throughout both lungs. Blood examination, December 24: hemoglobin, 60 per cent (Sahli), white cells, 10,480 per cmm, differential count, polynuclear leukocytes, 60 per cent, lymphocytes, 10 per cent, large mononuclears, 30 per cent, red cells, 3,610,000 per cmm. The urine contained a small amount of albumin and a few hyaline casts. The sputum was pneumonic in character and contained acid fast bacilli.

The patient ran a high temperature, varying about 2 degrees from morning to night. January 7 bronchial breathing developed in the right intrascapular region.

CASE 12—J S, white, boy, aged 12, was admitted to St Luke's Hospital Dec 7, 1917, and discharged recovered Jan 18, 1918.

Diagnosis: Fever of unknown cause.

The past medical history was unimportant. The present illness began one week prior to admission to the hospital, with diffuse abdominal pain, diarrhea and epistaxis. Later, malaise and lassitude developed. On physical examination, December 8, an enlarged, firm, smooth and nontender spleen was palpable at the left costal border. Otherwise physical examination was negative. Roentgenographic studies of the lungs were negative. Blood examination, December

8. hemoglobin, 72 per cent., white cells, 6,550 per cmm, differential count, polynuclear leukocytes, 68 per cent.; lymphocytes, 10 per cent.; large mononuclears, 22 per cent., red cells, 4,160,000 per cmm. The Widal reaction on two occasions was negative, as were also the blood cultures. Examinations of the urine and feces were negative.

The patient had two febrile periods of seven and eighteen days' duration separated by an interim of a week. He manifested no symptoms of severe toxemia in spite of a high fever. The enlarged spleen disappeared after the second febrile period had ended.

CASE 13—J. C., white, man, aged 30, was admitted to St. Luke's Hospital Nov. 24, 1917, and discharged recovered Dec. 31, 1917.

Diagnosis: Lobar pneumonia (Type IV)

The past medical history was unimportant. The present illness began one week prior to admission to the hospital, with a chill, pleuritic pain in the chest, cough and bloody, tenacious sputum. Physical examination, November 25, elicited the signs of pulmonary consolidation in the left infraclavicular fossa and the apex of the left axilla. The skin and the sclerae were icteric. Blood examination, November 26: hemoglobin, 60 per cent., white cells, 36,880 per cmm., differential count, polynuclear leukocytes 91 per cent., lymphocytes 5 per cent., large mononuclears 1 per cent., eosinophils, 1 per cent., mast cells, 2 per cent. Blood culture showed pneumococci belonging to Type IV. The Wassermann reaction was negative. Urine examinations showed a small amount of albumin and bilirubin. The sputum was typically pneumonic in type and was deeply bile stained.

The crisis occurred on the fourth day in the hospital. The icterus disappeared on the twelfth day. The signs of pulmonary consolidation had disappeared by December 8, both on physical examination and by the roentgen ray.

CASE 14—A. B., white, man, aged 23, was admitted to St. Luke's Hospital Nov. 22, 1917, and discharged recovered Dec. 13, 1917.

Diagnosis: Lobar pneumonia (stage of resolution)

No history was obtainable, due to the patient's inability to talk English. The patient entered the hospital during the pneumonic crisis. On physical examination, November 22, there were found the signs of pulmonary consolidation in the entire upper lobe of the right lung. There were numerous medium and fine crackling râles throughout this lung. There was some cough, with mucopurulent, bloody sputum. Blood examination, November 22: hemoglobin, 62 per cent., white cells, 8,160 per cmm., differential count, polynuclear leukocytes, 67 per cent., lymphocytes, 31 per cent., large mononuclears, 2 per cent. The Wassermann reaction was positive. The urine examinations were negative. Phenolsulphonephthalein excretion was 60 per cent. in two hours. The sputum was mucopurulent and slightly streaked with blood. It did not contain acid fast bacilli.

In about one week the cough and sputum ceased. By December 4 the signs of pulmonary consolidation had disappeared.

CASE 15—J. G., white, man, aged 35, was admitted to St. Luke's Hospital Dec. 17, 1917, and discharged recovered Jan. 4, 1918.

Diagnosis: Lobar pneumonia

The patient did not speak English and no history was obtained. On physical examination, December 18, signs of pulmonary consolidation were present in the apex of the right axilla, the right suprascapular fossa and the right intrascapular region. There was no cough and no expectoration. Blood examination, December 7: hemoglobin, 80 per cent.; white cells, 23,000 per cmm.; differential count, polynuclear leukocytes, 93 per cent., lymphocytes, 2 per

cent, large mononuclears, 5 per cent. Urine examinations showed occasionally a trace of albumin. Phenolsulphonephthalein excretion was 60 per cent in two hours.

The crisis occurred the third day in the hospital. The signs of pulmonary consolidation had almost disappeared by December 29, and on January 4 were no longer present.

CASE 16—P. D., white, boy, aged 20, was admitted to St. Luke's Hospital Nov. 17, 1917, and discharged recovered Jan. 11, 1918.

Diagnosis Typhoid fever.

The patient did not speak English and no history was obtained. The physical examination was essentially negative. Roentgenographic studies of the lungs were negative. The course of the disease was that of a case of typhoid fever with marked passive delirium. Blood examination, November 17: hemoglobin, 70 per cent; white cells, 5,040 per cmm; differential count, polynuclear leukocytes, 68 per cent; lymphocytes, 19 per cent; large mononuclears, 13 per cent. Two Widal reactions and two blood cultures were negative. The Wassermann reaction was negative. The urine contained a considerable amount of albumin throughout the period of fever, and also a variable number of casts. These findings disappeared after the fever subsided. Phenolsulphonephthalein excretion was 60 per cent in two hours. Examination of the feces was negative.

CASE 17—J. S., white, man, aged 35, was admitted to St. Luke's Hospital Oct. 4, 1917, and discharged recovered Nov. 15, 1917.

Diagnosis Typhoid fever.

The past medical history was unimportant. The present illness had begun five days prior to admission to the hospital, with malaise, lassitude, anorexia and epistaxis. During this period the patient was confined to bed. On physical examination, October 5, the liver and spleen were palpated at the costal margins. Otherwise the examination was essentially negative. Blood examination, October 5: hemoglobin, 70 per cent; white cells, 4,000 per cmm. The Widal reaction was positive in a dilution of 1:80. Urine examinations were negative. Phenolsulphonephthalein excretion was 60 per cent in two hours. The index of urea excretion (McLean) on October 15 was 119 per cent, and on November 1, 243 per cent. Blood urea nitrogen was 8 mg. per 100 c.c. of blood.

The patient had continuous fever for the first five days in the hospital. A recrudescence occurred from the fourteenth to the sixteenth days. The enlarged spleen disappeared with the approach of convalescence. There were no symptoms manifesting severe toxemia.

CASE 18—G. K., white, man, aged 37, was admitted to St. Luke's Hospital Oct. 2, 1917, and discharged recovered Nov. 10, 1917.

Diagnosis Typhoid fever.

The past medical history was unimportant. The patient had been confined to bed for the five days prior to admission to the hospital with headache, malaise, chilliness and feverishness. On physical examination, October 3, the spleen was palpated at the left costal margin. Otherwise the examination was essentially negative. Blood examination, October 3: hemoglobin, 80 per cent (Sahli); white cells, 5,000 per cm; the Widal reaction was negative. Urine examinations were negative except for an occasional trace of albumin. Phenolsulphonephthalein excretion was 50 per cent in two hours. The index of urea excretion (McLean) was 276 per cent on November 1, and the blood urea nitrogen was 7 mg. per 100 c.c.

The patient had fever while under observation for a period of nineteen days. There were no complications and no symptoms of severe toxemia. The enlarged spleen disappeared near the end of the febrile period.

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS

Case No	Day in Hos pital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
1	1					70			
	3	665	0 208	1 107	0 000		103 4 101 4	120 100	20 20
	4	1,025	0 308	1 707	0 855		102 4 99 6	112 100	24 22
	5	980	0 306	1 399	0 561		100 8 98 6	108 96	24 20
	6	570	0 169	0 785	0 184		102 0 97 4	100 88	24 14
	7	500	0 166	0 833	0 167		100 0 97 8	100 80	24 18
	8	850	0 324	0 944	0 271	62	99 8 97 0	112 92	24 18
	9	950	0 365	1 306	0 323		100 4 97 0	92 68	20 18
	10	350+	0 135+	0 438+	0 031+		100 0 97 6	104 80	20 18
	11	1,230	0 338	1 538	0 000		100 4 97 4	104 84	20 18
	12	905	0 328	1 158	0 000		99 8 97 0	108 72	24 18
	13	850	0 333	1 045	0 000	61 5	99 8 97 6	88 60	20 20
	14	965	0 454	1 129	0 000		99 0 97 6	92 76	20 20
	15	740	0 418	0 710	0 000		99 8 97 0	104 88	20 20
	16	1,085	0 532	1 064	0 000		100 0 97 0	102 84	22 20
	17	1,515	0 567	1 030	0 000		98 8 98 0	84 80	22 18
	18	1,145	0 508	1 113	0 000		98 0 97 0	80 78	20 18
	19	1,750	0 567	1 369	0 000		98 4 98 0	88 80	22 20
	20	1,190	0 386	0 932	0 000		99 0 97 0	92 80	22 22
	21	1,200	0 361	1 262	0 000		99 0 97 0	82 64	20 20
	22	1,515	0 585	1 257	0 000	62	98 0 97 0	84 72	20 20
	23	1,660	0 503	1 160	0 000		98 0 97 0	88 76	24 20
	24	1,695	0 469	1 146	0 000		100 0 97 0	88 64	20 18
	25	1,840	0 537	1 333	0 000		98 8 97 0	88 76	20 18
	26	1,405	0 445	1 033	0 000		98 0 97 0	76 64	20 18
	27	2,075	0 481	1 331	0 000		98 0 97 4	88 76	22 20

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
1 (cont)	28	1,535	0.408	1.031	0.000	64	98.0 97.0	84 76	20 20
	29	2,305	0.435	1.122	0.000		98.0 97.4	88 76	22 18
	30	1,135	0.313	0.885	0.000		99.0 97.8	80 76	24 24
	31	2,105	0.526	2.589	0.000		98.0 97.0	88 76	24 20
	32	2,055	0.485	1.309	0.000		98.6 97.0	80 74	22 20
	33	1,500	0.378	1.230	0.000		99.0 97.0	80 80	22 22
	34	1,820	0.484	1.281	0.000		98.6 97.0	88 80	20 20
	35	1,520	0.362	1.085	0.000		98.6 97.0	80 80	20 20
	36	2,350	0.470	1.204	0.000	66	97.0 97.0	84 80	20 20
2	1					59			
	2	710	0.422	0.985	0.436		104.0 103.0	102 92	24 20
	3	800	0.444	1.000	0.328		105.0 102.0	108 92	24 24
	4	925	0.467	1.165	0.240		103.8 102.0	112 72	24 24
	5	1,030	0.495	1.338	0.223		104.0 102.0	108 100	24 24
	6	1,530	0.819	1.818	0.249		104.0 102.4	112 96	28 24
	7	1,390	0.729	1.654	0.276		104.0 102.0	112 100	28 24
	8	1,470	0.771	1.633	0.250	58	104.0 101.8	118 88	26 24
	9	1,465	0.813	1.628	0.203		104.4 102.6	116 100	28 24
	10	1,300	0.755	1.625	0.231		104.6 102.8	128 100	34 24
	11	1,240	0.670	1.515	0.128		104.4 102.8	128 112	32 24
	12	995	0.683	1.154	0.219		104.0 101.8	136 112	30 24
	13	1,240	0.715	1.304	0.236		104.0 101.4	122 110	26 24
	14	1,340	0.834	1.241	0.334		100.4 100.0	124 100	24 24
	15	650	0.338	0.722	0.000	57	103.0 100.8	112 96	24 24

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
2 (cont)	16	1,235	0.635	1.503	0.020		101.8 99.8	120 88	24 22
	17	1,060	0.331	1.090	0.116		102.6 99.0	116 80	20 24
	18	1,070	0.310	1.124	0.064		100.4 98.0	100 84	24 24
	19	880	0.252	0.830	0.191		99.8 93.6	100 88	24 24
	20	1,400	0.448	1.600	0.116		99.0 98.6	100 80	24 24
	21	1,100	0.200	0.979	0.121		99.0 97.8	88 80	24 24
	22	1,180	0.363	1.090	0.090	54.7	99.0 98.0	84 80	20 20
	23	1,395	0.430	1.074	0.222		99.0 98.0	96 80	24 20
	24	2,005	0.539	1.082	0.690		99.0 97.8	103 80	24 20
	25	1,490	0.387	1.064	0.090		99.0 98.4	100 80	24 20
	26	1,770	0.833	1.011	0.099		99.4 98.4	100 80	24 18
	27	1,605	0.401	1.011	0.128		99.4 98.4	96 80	21 20
	28	1,615	0.349	1.153	0.090		102.0 93.4	94 80	24 20
	29	1,635	0.283	1.079	0.090	56.5	100.0 97.6	92 72	24 20
	30	1,095	0.276	1.054	0.090		99.4 98.4	92 84	24 20
	36					57			
	1					54.5			
	2	1,010	0.532	1.772	0.393		104.6 102.4	112 100	24 24
	4	2,005	0.783	2.223	0.090		105.0 103.0	120 103	24 24
	5	2,520	0.573	1.383	0.093		104.8 102.0	120 110	23 24
	6	2,965	0.705	2.411	0.295		104.6 102.8	120 103	28 24
	7	1,900	0.760	1.727	0.333		104.6 102.4	128 104	26 24
	8	2,645	0.777	1.762	0.340		104.4 102.8	124 103	28 24
	9	1,030	0.362	0.903	0.241	48	104.8 102.8	132 103	28 24
	10	1,515	0.765	1.515	0.321		104.4 103.0	132 104	28 24

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
3 (cont.)	11	1,130	0.583	1.478	0.371		104.4 102.8	126 106	28 24
	12	1,645	0.992	1.645	0.464		104.4 102.0	124 110	26 24
	13	1,450	0.541	1.291	0.348		104.4 102.0	126 112	26 24
	14	1,690	0.625	1.318	0.372		104.0 100.8	120 100	20 20
	15	1,340	0.523	1.175	0.459		103.8 101.4	120 100	24 22
	16	1,660	0.631	1.565	0.510		104.0 101.0	124 100	24 24
	17	1,005	0.383	0.824	0.352		103.6 101.4	124 100	24 24
	18	2,135	0.918	1.524	0.312	48	102.8 101.0	116 100	24 24
	19	1,130	0.471	0.831	0.300		102.8 99.0	108 100	24 24
	20	1,740	0.491	1.242	0.411		102.0 99.8	104 96	24 24
	21	1,810	0.500	1.158	0.344		103.0 99.4	120 80	24 20
	22	1,370	0.438	1.055	0.320		103.0 99.6	112 92	24 24
	23	1,470	0.406	1.035	0.190		102.8 99.0	110 92	24 24
	24	2,330	0.489	1.192	0.220		102.6 99.0	112 99	24 22
	25	1,110	0.317	0.855	0.154		102.6 99.6	108 100	24 24
	26	1,245	0.311	0.871	0.125		101.0 98.6	100 96	24 24
	27	1,435	0.321	0.890	0.129	45	100.0 99.0	104 92	24 20
	28	1,505	0.341	0.873	0.106		100.0 98.6	108 84	24 24
	29	1,155	0.289	0.866	0.096		100.0 98.6	108 84	24 24
	30	1,495	0.332	0.897	0.089		99.6 98.4	96 92	24 20
	31	1,445	0.275	0.850	0.104		100.0 98.6	116 96	24 24
	32	1,385	0.305	0.831	0.083		99.8 98.0	100 88	24 24
	33	1,740	0.386	0.887	0.122	44	99.0 98.0	100 92	24 24
	34	1,065	0.473	0.902	0.063		99.8 99.0	100 92	24 24

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
3 (cont)	35	1,580	0.342	0.585	0.000		99.0 97.8	94 92	24 24
	36	1,030	0.254	0.990	0.000		99.4 98.4	100 86	24 24
	37	1,155	0.328	0.962	0.000		99.4 98.4	100 84	24 24
4	1					58			
	3	1,260	0.433	0.764	0.270		101.0 100.0	108 96	28 24
	4	1,690	0.644	0.975	0.433		100.4 99.6	100 84	24 24
	5	920	0.465	0.534	0.239		100.0 99.6	104 84	24 20
	6	1,460	0.348	0.983	0.554		100.0 99.0	104 86	24 22
	7	1,640	0.263	1.077	0.423		100.0 99.0	102 88	24 24
	8	1,110	0.603	0.782	0.450		101.0 100.0	98 92	24 20
	9	1,430	0.595	1.021	0.722	53	101.0 100.0	108 92	26 24
	10	1,065	0.429	0.934	0.397		100.6 98.8	100 92	24 20
	11	1,230	0.425	1.025	0.256		100.0 99.4	108 96	24 22
	12	1,055	0.449	1.059	0.039		100.0 99.6	100 92	24 22
	13	635+	0.358+	0.635+	0.070+		100.0 98.0	100 88	24 20
	14	1,295	0.481	0.481	0.000		100.0 99.0	106 92	26 20
	15	1,075	0.546	0.895	0.000	53	100.0 98.6	100 92	24 20
	16	1,525	0.360	0.802	0.000		99.6 98.6	96 84	24 20
	17	1,645	0.382	1.096	0.000		100.0 98.0	92 80	20 20
	18	1,540	0.360	0.887	0.000		99.4 98.4	94 80	24 20
	19	1,350	0.235	0.860	0.000		99.0 97.6	88 72	22 20
	20	1,225	0.279	0.872	0.000		99.8 98.0	84 76	22 20
	21	1,565	0.290	0.972	0.000		100.0 98.0	92 84	24 20
	22	1,505	0.293	0.753	0.000		100.0 97.6	84 80	24 24
	23	1,040	0.213	0.732	0.000		99.4 98.4	84 80	24 24

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
4 (cont)	24	1,690	0 345	0 896	0 000	55 5	99 0 98 0	100 80	24 24
	25	1,060+	0 138+	0 498	0 000		99 0 98 0	80 68	20 20
	26	2,090	0 359	0 836	0 000		99 0 98 0	84 80	22 20
	27	2,220	0 555	0 844	0 000		99 0 98 4	80 78	22 22
	28	1,980	0 360	0 891	0 000		99 0 97 6	84 80	24 20
	29	2,260	0 305	0 981	0 000		99 0 98 4	84 80	24 24
5	1	755	0 265	1 178	0 398	58	101 0 101 0	90 84	24 24
	2	970	0 694	1 178	0 398		101 0 99 0	108 96	30 24
	3	970	0 584	1 469	0 000		99 0 98 0	104 76	28 24
	4	825	0 584	0 993	0 148		99 0 97 0	88 64	24 24
	5	965	0 314	1 072	0 134		98 6 97 6	86 60	24 20
	6	980	0 524	1 063	0 127	57	98 6 97 0	86 60	24 20
	7	1,720	0 593	1 536	0 134		98 0 97 0	84 56	20 18
	8	1,025	0 391	0 977	0 113		98 6 97 0	84 56	20 18
	9	1,110	0 221	1 356	0 000		98 8 97 0	72 68	20 18
	10	1,200	0 314	1 000	0 000		98 8 97 4	68 56	22 20
	11	1,455	0 342	1 323	0 000		98 0 97 8	64 56	22 18
	12	1,440	0 314	0 986	0 000		98 6 97 6	70 60	20 18
	13	1,970	0 406	1 447	0 000	57	98 6 98 0	64 52	20 18
	14	595?	?	?	0 000		99 0 98 0	68 52	20 20
	15	lost					99 4 98 6	64 60	20 18
	16	1,280	0 320	1 600	0 000		100 8 99 0	84 64	20 20
	17	885	0 278	1 106	0 000		100 8 98 6	88 80	20 20
	18	725	0 207	0 761	0 000		101 4 98 6	84 80	20 20
	19	500?	?	?	0 000		100 0 99 8	88 80	20 20

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
5 (cont)	20	1,065	0.213	1.325	0.000		103.0 99.8	100 80	24 24
	21	640?	?	?	0.000		102.8 99.8	100 80	24 24
	22	1,165	0.422	1.354	0.000		101.6 99.8	112 84	24 24
	23	1,065	0.309	1.416	0.000		103.4 100.0	100 88	26 24
	24	595?	?	?	0.000		103.6 100.0	100 88	26 24
	25	985	0.296	1.231	0.000		103.0 99.0	108 80	24 24
	26	970	0.258	1.241	0.000		102.6 99.0	112 88	24 24
	27	795	0.222	0.897	0.000	57	100.6 99.0	100 76	24 24
6	1					55.5			
	2	1,435	0.382	1.195			101.0 99.0	112 88	28 24
	3	1,000	0.286	1.428			100.4 98.6	100 88	28 20
	4	1,225	0.316	1.286			100.4 98.0	100 98	24 20
	5	1,710	0.414	1.485	0.000		100.6 99.0	100 88	24 20
	6	1,260	0.344	1.399	0.000		101.0 98.6	96 80	24 20
	7	1,355	0.343	1.693	0.000		100.8 97.0	96 80	30 20
	8	950	0.226	0.950	0.000		101.0 98.0	100 84	24 24
	9	845	0.218	1.082	0.000		100.0 98.8	96 80	26 20
	10	1,855	0.549	1.886	0.000		101.0 98.0	104 80	24 20
	11	1,200	0.374	1.132	0.000	55	101.0 97.4	116 80	24 20
	12	1,245	0.413	1.270	0.000		100.4 97.4	104 76	26 20
	13	1,590	0.374	1.272	0.000		100.4 97.6	104 84	26 20
	14	1,260	0.398	1.168	0.000		100.6 98.0	100 80	24 24
	15	1,435	0.495	1.121	0.184		100.0 99.0	92 84	24 20
	16	1,220	0.426	0.964	0.085		99.8 97.0	96 80	20 20

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in O e	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
6 (cont)	17	1,965	0.623	1.193	0.000		99.8 97.4	96 72	24 20
	18	1,490	0.709	1.550	0.000		99.6 97.0	84 74	22 20
	19	1,000	0.351	0.606	0.000		99.8 98.0	103 80	26 22
	20	1,185	0.624	0.823	0.000		100.6 98.0	96 76	24 24
	21	1,970	0.624	2.052	0.000		99.4 98.0	88 80	24 24
	22	2,095	0.468	1.360	0.052		99.4 97.6	92 76	24 24
	23	1,045	0.318	0.746	0.000		99.4 97.0	94 80	24 20
	24	2,315	0.659	1.928	0.000		99.0 98.0	100 76	24 20
	25	1,890	0.574	1.491	0.000	56.4	99.8 98.4	88 80	24 20
	26	2,030	0.498	1.326	0.000		100.6 98.0	80 64	24 20
	27	1,980	0.340	1.356	0.000		99.8 97.0	104 76	28 20
	28	1,845	0.442	1.229	0.000		99.4 97.0	100 76	24 20
	29	1,475	0.369	1.134	0.000		100.0 97.0	90 76	24 24
	30	2,110	0.511	1.319	0.000		98.0 97.0	80 74	24 20
	31	2,140	0.413	1.189	0.000	56.8	99.0 97.0	88 76	20 20
	32	1,530	0.370	1.233	0.000		99.0 97.4	84 76	24 20
	33	2,675	0.509	1.295	0.000		100.4 97.0	104 80	24 20
7	1					60.5			
	3	940	0.368	1.880	0.000		102.8 100.0	112 90	28 20
	4	300	0.125	0.624	0.090		102.0 100.0	116 104	28 22
	5	495	0.136	0.852	0.000		102.0 101.0	112 92	28 24
	6	535	0.214	1.027	0.160		102.6 99.0	120 88	30 22
	7	850	0.340	1.828	0.000	59	102.0 100.0	104 88	28 22
	8	630	0.265	0.958	0.000		102.6 100.4	112 96	28 20
	9	600	0.333	0.636	0.012		102.6 99.8	112 96	28 20

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hos pital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creat-inin in Gm	Crea-tin in Gm	Weight in Kg	Maximum and Minimum		
							Temper-ature, F	Pulse	Respira-tion
7 (cont.)	10	1,370	0 760	1 956	0 000		102 8 100 0	98 92	24 24
	11	895	0 497	1 395	0 000		103 0 100 0	100 92	28 24
	12	530	0 262	0 663	0 000		102 0 100 0	104 88	24 24
	13	1,315	0 644	1 879	0 000		102 0 99 4	104 92	28 24
	14	1,205	0 522	1 401	0 000		101 4 98 4	96 88	26 24
	15	1,860	0 791	1 281	0 000		102 4 99 0	92 80	24 24
	16	895	0 373	0 983	0 000	57	101 0 98 8	90 80	24 20
	17	1,260	0 531	1 679	0 000		101 0 98 0	100 98	26 24
	18	1,045	0 580	1 453	0 000		101 0 99 0	92 88	24 20
	19	820	0 480	1 040	0 000	57	100 4 98 6	92 76	28 20
	20	1,150	0 575	1 239	0 000		99 6 98 0	104 76	24 24
	21	1,235	0 413	1 107	0 000		100 0 98 4	90 80	24 24
	22	1,280	0 288	1 254	0 000		101 0 98 6	84 76	26 24
	23	2,195	0 442	1 462	0 000		100 0 99 0	90 76	28 24
	24	2,075	0 461	1 597	0 000		100 0 98 0	80 48	24 24
	25	1,740	0 435	1 390	0 000		100 0 98 4	88 76	24 20
	26	2,165	0 476	1 442	0 000		100 0 97 0	84 74	22 20
	27	1,430	0 358	1 191	0 000		99 6 98 0	96 80	20 20
	28	1,310	0 375	1 284	0 000	57	100 0 98 0	84 80	20 20
	29	1,230	0 377	1 168	0 000		100 0 97 8	82 80	22 22
	30	1,690	0 449	1 504	0 101		100 0 98 8	84 72	22 18
	31	1,690	0 436	1 301	0 000		100 0 98 0	92 72	20 20
	32	630	0 207	0 838	0 000		100 0 98 4	84 76	20 20
	33	1,115	0 297	1 035	0 000		99 4 98 6	80 64	20 18
8	2					56 4			

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hos pital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creat inin in Gm	Crea tin in Gm	Weight in Kg	Maximum and Minimum		
							Temper ature, F	Pulse	Respira tion
8 (cont)	3	1,785	0.723	2.173	0.111	51	104.6 101.0	102 72	24 20
	4	890	0.494	1.711	0.000		103.8 100.0	108 80	24 20
	5	840	0.484	1.389	0.000		103.6 99.6	88 68	24 20
	6	1,505	0.849	1.273	0.071		101.0 99.0	84 68	20 20
	7	1,555	0.524	1.233	0.000		99.0 98.0	72 56	20 18
	8	1,220	0.437	1.220	0.000		99.0 97.4	74 64	20 18
	9	1,135	0.407	0.813	0.038		99.0 97.6	56 44	20 18
	10	1,715	0.403	1.271	0.000		98.0 97.4	68 56	20 18
	11	1,835	0.382	1.207	0.000		99.0 97.0	80 76	24 20
	12	1,980	0.384	1.253	0.000		98.6 97.0	56 46	20 18
	13	1,760	0.305	1.085	0.032		98.6 97.6	52 40	20 18
	14	1,520	0.319	1.247	0.000		99.0 97.0	60 48	20 16
	15	1,650	0.252	0.999	0.000		99.8 97.0	66 60	22 20
	16	1,490	0.322	1.418	0.000		98.6 97.0	68 60	22 20
	17	2,440	0.356	1.220	0.000	55.5	99.6 97.8	60 56	20 20
	18	1,605	0.337	1.203	0.000		98.6 97.6	76 52	20 20
	19	1,985	0.256	1.113	0.000		98.6 97.4	54 48	18 16
9	1					58			
	2	815	0.282	1.630	0.000		100.4 99.0	92 80	24 24
	3	725	0.305	1.450	0.000		102.8 100.0	100 80	26 24
	4	875	0.364	1.093	0.000		101.0 99.6	94 80	24 24
	5	1,250	0.363	1.662	0.000		100.0 98.0	92 76	24 24
	6	1,075	0.325	1.247	0.000		99.8 98.0	80 72	24 24
	7	960	0.307	1.449	0.000		99.4 98.4	80 64	24 24
	8	1,085	0.304	1.550	0.000		99.6 98.4	80 64	22 20

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hos pital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
9 (cont)	9	1,510	0 380	1 676	0 000	58	100 0 98 4	80 68	20 18
	10	1,020	0 271	1 132	0 000		102 0 98 8	80 64	24 24
	11	1,800	0 367	1 800	0 000		99 0 98 6	80 64	24 24
	12	1,520	0 328	1 520	0 000		99 4 98 6	80 64	24 24
	13	1,330	0 287	0 838	0 000		99 8 98 4	80 60	24 18
	14	1,500	0 302	1 363	0 000		99 0 98 0	80 72	24 24
	15	1,410	0 268	1 128	0 000		99 0 98 6	72 60	20 20
	16	1,120	0 193	1 018	0 000		99 4 98 4	72 64	20 20
	17	2,135	0 405	1 836	0 000		99 4 98 0	92 60	24 24
	18	1,475	0 319	1 287	0 000		98 8 98 0	80 72	24 24
	19	2,000	0 554	1 538	0 000	58	98 8 98 4	74 60	24 24
	20	800	0 262	0 869	0 000		99 8 98 4	74 60	24 24
	21	1,295	0 204	1 439	0 000		98 6 97 6	68 60	24 24
	22	1,655	0 320	1 793	0 000		98 6 98 0	72 72	24 24
	23	1,380	0 299	1 254	0 000		98 6 98 6	68 68	24 24
	2					54			
	3	790	0 465	1 286	0 000		102 8 102 0	112 100	28 28
	4	735	0 282	1 049	0 118		103 0 100 8	112 100	28 28
	5	630	0 494	1 050	0 525		103 0 101 4	112 92	28 26
	6	490+	0 415+	0 650+	0 413+		103 0 101 6	110 96	28 26
	7	770	0 638	1 070	0 470	51	102 8 101 4	102 96	28 26
	8	520+	0 298+	0 741+	0 468+		102 6 100 6	108 100	28 28
	9	340+	0 291+	0 607+	0 364+		102 6 101 0	104 96	26. 26
	10	710	1 065	1 291	0 577		102 6 100 6	108 100	28 28

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
11	2					48.6			
	9					45			
	11	820	0.455	0.960	0.000		102.6 100.0	112 96	26 26
	12	580	0.358	0.722	0.000		102.0 100.0	124 96	28 26
	13	650	0.421	0.812	0.000		102.4 100.0	112 88	30 26
	14	680	0.219	0.750	0.000		102.8 100.0	120 88	30 26
	15	605	?	0.756	0.000		103.0 100.0	132 100	44 30
	16	lost				45	103.0 100.0	128 116	32 28
	17	740	0.440	0.967	0.000		103.0 102.0	132 112	40 32
	18	590	0.378	0.758	0.000		102.6 100.0	132 104	36 32
	19	980	0.628	0.859	0.000		103.6 100.4	132 103	32 28
	20	1,055	0.535	0.886	0.000		103.0 100.0	124 100	28 28
	21	540	?	0.540+	0.136+		103.4 99.0	124 118	28 28
	24	1,110	0.756	1.000	0.000	45	102.8 99.0	120 96	28 26
	25	1,120	0.612	0.855	0.000		102.0 100.0	110 88	26 24
	26	650	0.580	0.812	0.000		102.0 100.0	112 96	28 26
	28	900	0.562	0.909	0.000		102.0 99.8	104 96	28 28
12	2					26.4			
	7	955	0.273	0.542	0.139		102.0 97.8	116 80	24 24
	8	900	0.247	0.473	0.107		101.0 98.0	100 80	24 22
	9	905	0.237	0.362	0.045	27.7	99.0 98.4	96 80	24 24
	10	1,335	0.312	0.494	0.093		99.0 97.8	100 80	24 22
	11	1,860	0.298	0.465	0.037		99.0 98.4	92 98.4	24 22
	12	1,370	0.353	0.630	0.000		99.6 98.6	104 80	24 22
	13	1,580	0.262	0.600	0.000		99.6 98.6	88 80	22 20
	14	1,320	0.230	0.523	0.000		100.0 98.6	112 80	24 20

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in G c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
12 (cont)	15	1,355	0 190	0 501	0 000	31 8	102 0 99 0	124 80	28 20
	16	1,745	0 454	0 820	0 000		103 8 100 8	132 108	20 24
	17	770+	?	?	0 039+		104 4 102 0	144 100	28 24
	18	680+	?	?	0 126+		103 6 101 6	128 104	30 24
	19	1,035	0 228	0 517	0 053		104 0 102 0	128 92	30 24
	20	1,165	0 238	0 641	0 128		103 4 100 6	126 108	24 24
	21	Lost					103 0 98 4	120 92	24 24
	22	1,335	0 254	0 668	0 260		102 0 98 6	124 92	24 24
	23	1,245	0 187	0 401	0 187		101 0 97 8	104 90	24 24
	24	1,255	0 196	0 402	0 100		100 8 97 4	88 80	24 24
	25	1,285	0 276	0 510	0 056	29	100 0 97 4	92 84	24 24
	26	1,375	0 261	0 491	0 000		98 6 97 4	80 88	24 24
	27	810	?	0 336	0 046		99 0 97 4	88 80	24 24
	28	1,235	0 152	0 449	0 055		98 8 97 8	84 68	24 24
	29	1,535	0 307	0 421	0 045		98 6 97 8	84 76	24 24
	30	1,385	0 204	0 449	0 023		98 6 97 6	80 72	24 24
	31	1,355	0 194	0 386	0 000		99 0 98 0	96 92	24 24
	32	875	?	0 355	0 000		98 6 98 4	84 80	24 24
	33	1,355	0 329	0 430	0 040	30	98 6 98 0	84 80	24 24
	34	1,530	0 318	0 424	0 071		99 0 97 8	88 80	24 24
	35	1,010	0 509	0 323	0 064		98 6 97 6	84 80	24 24
	36	1,595	0 295	0 470	0 061		98 6 98 4	96 76	24 24
	37	1,020	0 265	0 400	0 057		101 0 98 0	88 80	24 24
	39					31 4			

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
13	1					56			
	2	1,215	0.530	1.276	0.547		104.0 100.6	128 104	48 36
	3	1,420	0.861	1.291	0.982		105.0 102.8	132 120	32 28
	4	1,410	0.939	1.282	0.792		128.0 88.0	128 88	30 20
	5	1,170	0.779	1.064	0.692		101.0 99.8	102 76	30 26
	6	1,110	0.778	1.232	0.899		100.8 99.0	100 72	30 22
	7	770	0.494	1.099	0.650		99.8 99.0	96 60	32 24
	8	1,185	0.493	1.148	1.097		99.8 98.6	68 60	28 20
	9	890	0.722	1.269	0.666		100.0 98.0	80 64	24 20
	10	920	0.767	1.045	0.737	51.8	99.0 98.6	76 60	24 20
	11	650	0.591	0.764	0.319		99.0 97.8	83 56	28 20
	12	1,220	0.813	1.108	0.855		100.6 98.0	70 56	24 20
	13	820	0.452	0.966	0.248		99.0 97.0	72 60	24 20
	14	555+	?	0.673+	0.318+		99.0 97.0	60 44	20 20
	15	850	0.488	1.207	0.000		98.8 97.0	70 50	24 18
	16	905	0.529	0.983	0.148		98.6 97.0	62 62	20 18
	17	1,185	0.327	0.912	0.000	52.3	99.0 97.8	52 48	20 20
	18	1,050	0.317	1.050	0.000		99.0 97.6	70 56	22 18
	19	1,495	0.434	1.151	0.000		99.4 97.0	70 52	20 18
	20	735	0.196	0.816	0.000		99.4 98.0	76 60	24 20
	21	940	0.290	1.147	0.000		100.0 97.8	76 60	20 20
	22	1,245	0.384	1.132	0.000		99.4 97.6	76 60	20 20
	23	985	0.371	1.034	0.000		99.0 97.8	76 60	20 20
	24	1,420	0.298	0.916	0.000	55.5	99.0 97.6	72 60	20 18

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hos pital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creat-inin in Gm	Crea-tin in Gm	Weight in Kg	Maximum and Minimum		
							Temper-ature, F	Pulse	Respira-tion
14	1					55.5			
	2	1,140	0.414	0.950	0.095		99.8 97.8	80 60	30 20
	3	1,150	0.460	0.756	0.337		98.6 97.6	68 52	20 18
	4	2,765	1.136	1.535	0.539		98.4 97.8	80 56	20 18
	5	1,970	0.636	1.037	0.412		102.6 97.8	86 52	24 20
	6	1,935	0.549	1.105	0.482		98.0 97.6	64 48	22 18
	7	1,850	0.508	1.265	0.301		98.6 98.0	64 52	22 18
	8	1,845	0.481	1.164	0.362		98.6 97.8	60 52	20 16
	9	2,025	0.810	1.841	0.409		98.0 97.0	72 50	22 18
	10	1,320	0.419	1.145	0.175		98.6 98.0	62 60	20 20
	11	1,520	0.496	1.408	0.000	52.3	99.4 98.0	60 52	20 18
	12	2,115	0.589	1.438	0.000		99.0 97.0	60 46	20 16
	13	1,250	0.356	0.951	0.185		98.6 97.0	72 50	20 18
	14	1,845	0.419	1.317	0.124	52.3	99.0 97.6	62 44	24 18
	15	1,310	0.304	0.872	0.097		99.0 98.0	52 46	20 18
	16	1,715	0.408	1.271	0.000		99.0 97.0	52 46	18 18
	17	1,825	0.416	1.293	0.000		98.6 97.4	60 52	22 18
	18	1,575	0.295	1.125	0.000		98.6 97.0	52 44	20 18
	19	1,885	0.346	1.327	0.000		99.0 97.0	52 50	18 18
	20	1,435	0.276	1.879	0.000		98.8 97.0	60 52	18 18
15	2	1,285	0.702	1.799	0.257	54.5	104.0 102.6	112 100	32 30
	3	1,110	0.670	1.354	0.000		102.4 97.0	104 72	30 26
	4	1,090	0.519	0.894	0.000		98.6 97.0	84 72	26 20
	5	720	0.281	0.621	0.000		100.0 97.0	84 56	26 20
	6	1,210	0.332	0.932	0.000		98.6 96.4	84 52	28 24

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Creatinin in Gm	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
15 (cont)	7	1,590	0.382	1.192	0.000		98.0 96.0	72 60	24 24
	8	935	0.302	0.982	0.000	53	99.0 97.0	72 60	24 24
	9	820	0.248	0.861	0.000		100.0 97.0	72 52	24 20
16	1					56.4			
	14					49.5			
	24					48			
	27	1,920	0.545	0.720	0.161		99.4 98.4	88 72	24 20
	28	2,210	0.544	0.914	0.136		99.0 97.6	84 64	24 22
	29	1,575	0.387	0.605	0.061		98.6 98.0	81 68	22 22
	30	2,130	0.609	0.895	0.000		99.0 97.6	81 56	20 20
	31	1,805	0.451	0.794	0.000		99.0 97.8	80 74	20 20
	32	1,410	0.329	0.671	0.000	45.4	98.8 97.0	80 68	20 20
	33	2,125	0.497	0.748	0.000		99.4 98.0	80 56	20 20
	34	1,860	0.495	0.874	0.000		99.4 97.8	70 60	20 18
	35	2,105	0.493	0.956	0.000		99.6 98.0	72 56	20 20
	36	1,335	0.296	0.621	0.000		99.4 97.4	68 52	20 18
	37	1,995	0.407	0.866	0.000		100.0 98.6	76 64	20 18
	38	2,225	0.387	0.934	0.000		100.0 98.6	76 72	22 20
	39	2,250	0.392	0.843	0.000	48	99.0 98.4	72 56	20 18
	40	1,990	0.370	0.915	0.000		99.0 99.0	72 56	20 20
17				Gm of P ₂ O ₅ Excreted in 24 Hrs					
	10	2,050	0.937				100.0 98.0	90 80	
	11	1,440	0.655	2.476		58	100.0 98.6	80 75	
	12	1,540	0.762	2.883			99.0 98.0	80 60	
	13	1,420	0.551	2.633			99.0 98.0	70 60	

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in C c	Uric Acid in Gm	Gm of P_2O_5 Excreted in 24 Hrs	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
17 (cont.)	14	1,610	0.805	3.274			99.0 97.0	70 60	
	15	1,390	0.610	2.312			99.0 97.0	80 60	
	16	1,570	0.618	2.450			99.0 98.0	80 70	
	17	1,460	0.658	2.686			99.6 97.6	90 60	
	18	1,205	0.385	2.217		57	99.0 97.4	75 65	
	19	1,810	0.601	2.329			98.6 97.0	90 60	
	20	1,565	0.623				102.4 97.0	110 70	
	21	1,565	0.623	2.054			104.4 102.4	120 100	
	22	2,370	0.568	3.381			101.0 98.6	100 80	
	23	2,000	0.564	1.288		57	98.8 98.0	85 60	
	24	655	0.328	1.085			99.6 97.0	70 60	
	25	1,970	0.656	2.170			99.8 98.0	85 70	
	26	2,885	0.481	4.877			99.0 97.6	80 70	
	27	2,200	0.411	1.872			99.4 97.4	85 70	
	28	3,000	0.458	1.552			99.0 97.0	80 60	
	29	2,430	0.463	1.257			98.6 97.8	80 60	
	30	1,915	0.471	2.288		53.5	99.0 97.0	80 70	
	31	Lost							
	32	2,585	0.512	3.068			99.0 97.0	80 60	
	33	1,775	0.384	2.530			98.8 97.0	65 60	
	34	1,980	0.390				99.4 97.0	80 65	
	35	2,165	0.413			58	98.6 97.0	80 70	
	36	1,615	0.306				99.4 97.0	85 65	
	37	1,975	0.362				99.0 97.0	80 70	
	38	1,930	0.351				99.0 97.0	80 60	

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in Cc	Uric Acid in Gm	Gm of P_2O_5 Excreted in 24 Hrs	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
18	10	990	0.681	0.353			102.6 99.6	95 75	
	11	1,090	0.579	1.020		64.5	102.0 100.6	100 80	
	12	540	0.338	0.412			101.4 100.0	100 80	
	13	770	0.513	1.245			101.4 99.4	100 90	
	14	570	0.456	0.668			102.0 100.0	90 75	
	15	850	0.566	1.172			102.4 100.0	95 70	
	16	760	0.528	1.258			102.4 101.0	98 70	
	17	450	0.322	1.071			102.4 100.0	85 70	
	18	500	0.410	0.920			102.0 100.0	85 75	
	19	680	0.485	1.080			101.0 98.0	90 65	
	20	1,090	0.708	1.112		64.5	101.0 99.4	100 65	
	21	850	0.506				101.4 99.0	80 60	
	22	850	0.506	1.286			100.0 98.0	70 60	
	23	1,430	0.681	1.511			98.8 97.0	70 55	
	24	1,570	0.809	1.299			98.6 97.0	80 55	
	25	1,180	0.625				98.8 97.0	70 55	
	26	1,900	0.819	1.923			98.6 98.0	70 60	
	27	2,985	0.670	1.470			98.0 97.6	70 60	
	28	2,530	0.582	2.152			98.6 97.6	80 60	
	29	3,770	0.710	1.848		63	99.0 97.4	95 55	
	30	2,520	0.536	1.305			98.6 97.0	75 60	
	31	1,565	0.425	2.265			98.0 97.6	70 55	
	32	1,085	0.516	2.186			97.8 97.0	90 55	
	33	1,740	0.442				97.6 97.0	65 55	

URINARY CREATIN, CREATININ, AND URIC ACID IN FEVERS—(Continued)

Case No	Day in Hospital	Amount of Urine in 24 Hrs in Cc.	Uric Acid in Gm	Gm of P_2O_5 Excreted in 24 Hrs	Creatin in Gm	Weight in Kg	Maximum and Minimum		
							Temperature, F	Pulse	Respiration
18 (cont.)	24	1,505	0.335		.	.	98.0 97.0	75 55	
	25	1,550	0.391				98.4 97.0	85 60	
	26	1,435	0.236		.	62	98.0 97.0	100 60	
	27	1,020	0.212				98.6 97.0	70 60	
	28	2,055	0.412	.	.	.	98.6 97.0	70 60	
	29	1,155	0.291		.		97.4 97.0	80 60	
	43	.	.		.	64			

THE COMPARATIVE FOOD VALUE OF PROTEIN, FAT AND ALCOHOL IN DIABETES MELLITUS AS MEASURED BY THE NITROGEN EQUILIBRIUM *

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In a previous publication¹ it was claimed that probably the lowest diet which will conserve the physical and mental efficiency of the diabetic is that which maintains the nitrogen equilibrium of the patient. The experiments reported at that time showed that on a so-called carbohydrate-free diet, in which the proteins and fat were approximately equal to each other, gram for gram, maintenance, as measured by the nitrogen balance, was obtained at from 1,500 to 2,000 calories, the variations usually depending on the size and the sex of the patient. No attempts were made to determine which of the ingredients of a starch-free dietary, fat, protein or alcohol, was the most efficient protein sparer. In order to administer a diet of as low caloric value as possible, and still establish maintenance, it is essential to have this information.

The aim of the present investigation is to determine the comparative value of protein, fat and alcohol as nitrogen spacers, when added to the "carbohydrate-free" diet in diabetes mellitus. The patients observed were given diets of a constant protein, fat and starch content, and of such caloric value that there was a negative nitrogen balance. The fats and proteins were approximately equal to each other, gram for gram, the carbohydrates were those unavoidably present in the green vegetables. This constituted the control period, it was usually kept up for six days. Subsequently, definite amounts of protein, fat and alcohol were added to the dietary, and the effect on the nitrogen balance noted. The methods were the same as previously employed.¹ One of the experiments is presented in detail in Table 1. All the other cases were studied by similar methods, but only a summary of the findings is given in Tables 2 and 3.

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* From the Medical Clinic of The Johns Hopkins Hospital

¹ Mosenthal, H O, and Clausen, S W. THE ARCHIVES INT MED, 1918, 21, 269

TABLE 1—DIABETIC DATA FROM THE OBSERVATIONS ON A CASE OF DIABETIS MELITUS, MALE, AGED 47, HEIGHT, 177 CM THIS IS AN EXAMPLE OF THE EXPERIMENTS AS CARRIED OUT IN EACH OF THE CASES, A SUMMARY ONLY
BEING PRESENTED IN TABLES 2 AND 3

Date	Urine			Feces Nitro- gen, Gm	N Output, Gm	N Intake, Gm	N Balance, Gm	Food, Gm *				Calories			Weight, kg
	Glu- cose, Gm	Acetone Bodies as Body, Gm	Nitro- gen, Gm					Pro- tein	Fat	Carbohy- drate	Alco- hol	Total	Per kg per Day	Per Sq M per Hour	
1/ 2/18	0	9.03	10.08	1.12	11.50	11.50	0	71.9	70.3	12.7	0	1,001	19.3	25.0	51.9
1/ 3/18	0	20.57	12.57	1.12	13.99	11.12	-2.57	71.1	70.5	12.6	0	1,000	18.9	25.3	52.9
1/ 4/18	0	19.16	10.25	1.12	11.67	11.47	-0.20	71.7	70.3	12.7	0	1,000	18.7	25.1	53.0
1/ 5/18	0	25.71	17.03	1.12	18.15	11.16	-6.99	71.6	70.1	12.6	0	1,000	19.0	25.1	52.5
1/ 6/18	0	20.91	12.94	1.12	11.36	11.17	-2.89	71.7	70.2	12.9	0	1,000	19.2	25.3	52.0
1/ 7/18	0	13.01	12.57	1.12	13.93	11.11	-2.55	71.3	70.7	12.3	0	1,000	19.6	21.1	50.9
1/ 8/18	0	16.90	11.52	2.73	11.25	11.50	-2.75	71.9	70.1	12.3	71.4	1,500	29.1	38.7	51.0
1/ 9/18	0	5.50	11.22	2.73	13.05	11.59	-2.56	71.2	70.8	12.2	71.4	1,500	29.7	38.5	50.5
1/10/18	0	11.00	10.11	2.73	12.87	11.17	-1.10	71.7	70.3	12.6	71.4	1,199	29.6	38.5	50.6
1/11/18	0	5.65	12.60	2.73	15.33	11.16	-3.57	71.0	70.1	12.7	71.4	1,500	30.1	39.2	49.3
1/12/18	0	6.10	7.63	2.73	10.36	11.16	1.10	71.0	70.5	12.3	71.4	1,199	30.8	39.8	48.7
1/13/18	0	6.10	10.76	2.73	13.19	11.11	-2.08	71.3	70.8	12.2	71.4	1,501	30.0	39.0	50.0
1/14/18	0	1.39	9.52	1.99	11.51	11.36	-0.15	71.0	125.1	12.1	0	1,501	50.3	39.3	49.5
1/15/18	0	6.79	12.10	1.99	11.09	11.36	-2.73	71.0	125.0	12.0	0	1,503	30.1	39.0	49.9
1/16/18	0	6.83	10.71	1.99	12.73	11.36	-1.37	71.0	125.4	12.0	0	1,507	30.7	39.1	49.1
1/17/18	0	6.04	11.56	1.99	13.15	11.35	-1.97	71.1	125.2	12.0	0	1,505	31.2	39.6	48.8
1/18/18	0	5.29	11.39	1.99	13.38	11.35	-2.00	71.1	125.1	12.0	0	1,504	30.8	39.9	48.7
1/19/18	0	7.88	13.95	1.99	15.94	11.39	-1.55	71.3	125.0	12.1	0	1,504	30.6	39.3	49.2
1/20/18	0	8.10	13.95	2.66	16.61	21.00	17.59	150.0	89.2	13.3	0	1,199	31.1	39.6	48.7
1/21/18	0	10.93	11.65	2.66	17.31	21.02	16.71	150.1	89.3	13.1	0	1,501	31.0	39.6	48.4
1/22/18	0	5.05	11.97	2.66	11.63	21.05	19.12	150.3	89.1	13.3	0	1,199	31.2	39.6	48.0
1/23/18	0	5.17	12.58	2.66	15.21	21.02	15.78	150.1	89.1	13.1	0	1,501	30.7	39.9	48.7
1/24/18	0	9.31	11.29	2.66	15.95	21.02	10.07	150.1	89.1	13.2	0	1,501	31.3	39.7	47.9
4/25/18	0	5.67	11.09	2.66	13.75	21.02	10.27	150.1	89.5	13.1	0	1,502	30.1	39.0	48.7

TABLE 2—CONDENSED DATA FROM CASES OF DIABETES MELLITUS ON CARBOHYDRATE-FREE DIETS, SHOWING THE COMPARATIVE VALUE OF PROTEIN, FAT AND ALCOHOL AS NITROGEN SPARERS THE DAILY FOOD WAS CONSTANT DURING EACH PERIOD

Patient	Period Days	Glyco- suria, Gm per Day	Nitrogen, Gm per Day			Food, Gm per Day *				Calories			Acetone Bodies in Urine as B o n y, Gm per Day
			Intake	Output (Urine and Feces)	Balance	Pro- tein	Fat	Carbo- hydrate	Alco- hol	Total per Day	Per Kilo per Day	Per Sq M per Hour	
Case 1 Medical History No 39566 Male, aged 63 Height, 170 cm (5 ft 7 in) Weight, 70 kg (154 lbs)	6	0	11.4	14.2	-2.8	71.4	70.5	12.3	0	999	14.3	23.0	12.7
	6	0	11.4	14.4	-3.0	71.5	70.4	12.4	71.4	1,499	21.4	34.5	12.7
	6	0	11.4	11.9	-0.5	71.3	125.1	12.1	0	1,505	21.5	34.7	8.0
	6	0	11.5	12.4	-0.9	71.7	70.6	12.4	0	1,001	14.3	23.0	9.1
	6	0	11.4	13.7	-2.3	71.1	125.2	12.1	0	1,506	21.5	34.7	9.9
	6	0	11.4	13.9	-2.5	71.4	70.5	12.4	71.4	1,499	21.4	34.5	10.5
	6	0	24.1	18.3	+5.8	150.3	89.3	13.5	0	1,502	21.5	34.6	9.8
Case 2 Medical History No 39536 Male, aged 47 Height, 177 cm (5 ft 10 in) Weight, 50 kg (110 lbs)	6	0	11.5	14.0	-2.5	71.6	70.4	12.6	0	1,000	20.0	25.8	18.1
	6	0	11.4	13.4	-2.0	71.5	70.5	12.4	71.4	1,499	30.0	38.7	9.5
	6	0	11.4	13.5	-2.1	71.1	125.2	12.0	0	1,505	30.1	38.8	6.2
	6	0	24.0	15.3	+8.7	150.1	89.3	13.2	0	1,500	30.0	38.7	7.9
Case 3 Medical History No 39300 Male, aged 22 Height, 172 cm (5 ft 8 in) Weight, 52 kg (114 lbs)	6	0	11.4	14.4	-3.0	71.5	70.5	12.4	0	1,000	19.2	25.9	
	6	0	11.5	13.8	-2.3	71.6	70.5	12.5	71.4	1,500	28.9	38.9	8.8
	6	0	11.4	14.3	-2.9	71.4	125.2	12.2	0	1,507	29.0	39.0	7.2
	6	0	11.4	12.7	-1.3	71.5	70.4	12.8	0	1,000	19.2	25.9	9.9
	6	0	24.0	25.1	-1.1	150.2	143.2	13.3	0	2,002	38.5	51.9	9.3
	6	0	24.1	24.9	-0.8	150.4	143.2	25.3	0	2,052	39.5	53.2	11.2
Case 4 Medical History No 38448 Male, aged 33 Height, 177 cm (5 ft 10 in) Weight, 60 kg (132 lbs)	6	0	11.5	12.1	-0.6	71.6	70.5	12.5	0	1,000	16.7	23.9	
	6	0	11.4	13.3	-1.9	71.5	70.4	12.4	71.4	1,499	25.0	35.8	10.2
	6	0	11.4	12.9	-1.5	71.2	125.2	12.1	0	1,506	25.1	36.0	8.8
	6	0	24.0	19.1	+4.9	150.2	89.2	13.5	0	1,501	25.0	35.8	12.3

<p>Case 5 Medical History No 33079 Male, aged 59 Height, 163 cm (5 ft 4 in) Weight, 47 kg. (103 lbs)</p>	3	0	11.6	14.3	-2.7	72.2	70.2	12.2	0	939	21.3	28.1
	6	0	11.6	13.3	-1.7	72.5	70.2	12.4	37.6	1,264	26.9	35.5
	6	0	11.6	13.3	-1.7	72.2	70.3	12.1	0	939	21.3	28.1
	6	0	11.4	10.2	+1.2	71.3	125.4	12.1	0	1,508	32.1	42.4
	6	0	11.4	11.9	-0.5	71.4	125.3	12.6	37.6	1,773	37.7	49.8
	6	0	24.0	18.4	+5.6	150.2	89.4	13.1	0	1,501	31.9	42.2
	6	0	11.5	14.9	-3.4	71.7	70.3	12.5	37.6	1,262	26.9	35.5
	6	0	11.4	12.1	-0.7	71.2	125.1	12.1	0	1,505	32.0	42.3
	6	0	11.4	12.5	-1.1	71.3	70.4	12.8	0	1,000	21.3	28.1
	6	0	24.1	21.5	+2.6	150.6	89.2	13.4	0	1,502	32.0	42.2
	6	0	11.4	14.6	-3.1	71.2	125.2	12.1	0	1,506	32.0	42.3
	6	0	11.5	13.7	-2.2	71.6	70.4	12.3	71.4	1,439	31.9	42.1
	6	0	11.4	12.3	-0.9	71.2	125.2	12.2	71.4	2,006	42.7	56.4
	6	0	11.4	14.4	-3.0	71.5	70.5	12.4	0	1,000	17.9	25.0
<p>Case 6 Medical History No 33254 Male, aged 55 Height, 173 cm (5 ft 8 in) Weight, 56 kg (123 lbs)</p>	6	0	11.4	14.4	-3.0	71.5	70.5	12.4	0	1,000	17.9	25.0
	6	0	11.5	13.8	-2.3	71.6	70.5	12.5	71.4	1,500	26.8	37.5
	6	0	11.4	14.3	-2.9	71.4	125.2	12.2	0	1,507	26.9	37.7
	6	0	11.4	12.7	-1.3	71.5	70.4	12.8	0	1,000	17.9	25.0
	6	0	11.4	13.7	-2.3	71.2	125.3	12.4	0	1,508	26.9	37.7
	6	0	11.5	14.2	-2.7	71.6	70.5	12.5	71.4	1,500	26.8	37.5
	8	0	24.0	20.3	+3.7	150.1	89.3	13.3	0	1,500	26.8	37.5
	6	0	24.0	24.6	-0.6	150.1	89.5	13.3	35.5	1,751	31.3	43.8
	6	0	24.0	21.2	+2.8	150.1	118.2	13.2	0	1,750	31.3	43.7
	8	0	11.5	14.4	-2.9	71.8	70.4	12.5	0	1,000	25.0	29.6
	6	0	11.4	11.9	-0.5	71.5	70.5	12.6	71.4	1,500	37.5	44.4
	6	0	11.1	10.2	+1.2	71.2	126.6	12.4	0	1,520	38.0	45.0
	6	12.0	11.5	12.4	-0.9	71.6	70.6	12.5	0	1,001	25.0	20.6
	1	7.0	11.1	9.7	+1.7	71.4	125.4	12.2	0	1,509	37.7	44.6
<p>Case 7 Medical History No 33176 Male, aged 23 Height, 167 cm (5 ft 6 in) Weight, 40 kg (88 lbs)</p>	8	0	11.5	14.4	-2.9	71.8	70.4	12.5	0	1,000	25.0	29.6
	6	0	11.4	11.9	-0.5	71.5	70.5	12.6	71.4	1,500	37.5	44.4
	6	0	11.1	10.2	+1.2	71.2	126.6	12.4	0	1,520	38.0	45.0
	6	12.0	11.5	12.4	-0.9	71.6	70.6	12.5	0	1,001	25.0	20.6
	1	7.0	11.1	9.7	+1.7	71.4	125.4	12.2	0	1,509	37.7	44.6

* The articles of food printed in heavy type indicate the addition to the control diet

TABLE 2—CONDENSED DATA FROM CASES OF DIABETIS MELLITUS ON CARBOHYDRATE-FREE DIETS, SHOWING THE COMPARATIVE VALUE OF PROTEIN, FAT AND ALCOHOL AS NITROGEN SPARERS THE DAILY FOOD WAS CONSTANT DURING EACH PERIOD—(Continued)

Patient	Period Days	Glyco- sulph., Gm per Day	Nitrogen, Gm per Day			Food, Gm per Day *				Calories			Acetone Bodies in Urine as Body, Gm per Day
			Intake	Output (Urine and Feces)	Balance	Pro- tein	Fat	Carbo- hydrate	Alco- hol	Total per Day	Per Kilo per Day	Per Sq M per Hour	
Case 8 Medical History No 38890 Male, aged 35 Height, 158 cm (5 ft 2 in) Weight, 43 kg (95 lbs)	7	0	115	130	-15	71.9	70.2	12.1	0	997	23.2	29.7	
	7	0	114	113	-29	71.1	70.7	12.2	37.6	1,263	29.1	37.6	
	6	0	114	127	-13	71.3	125.4	12.4	0	1,509	35.1	11.9	
	6	0	24.1	18.0	+6.1	150.3	89.7	13.3	0	1,505	35.0	44.8	
	6	0	114	131	-17	71.5	70.3	12.5	37.6	1,261	29.3	37.6	
	6	0	115	113	+0.2	71.6	70.4	12.4	0	999	23.2	29.7	
	6	0	24.0	18.3	+5.7	150.2	89.1	13.5	0	1,503	35.0	44.8	
	4	0	114	118	-3.4	71.1	125.6	12.0	0	1,510	35.1	44.9	
Case 9 Medical History No 38896 Male, aged 52 Height, 169 cm (5 ft 7 in) Weight, 44 kg (97 lbs)	3	0	117	128	-11	73.3	70.4	10.8	0	1,000	22.7	28.2	
	3	0	115	133	-18	71.8	70.4	12.3	37.6	1,263	28.7	35.6	
	3	0	114	129	-15	71.2	70.3	12.3	0	996	22.6	28.1	
	6	0	116	124	-0.8	72.4	70.2	12.1	37.6	1,264	28.7	35.6	
	6	0	116	124	-0.8	72.3	70.4	12.2	0	1,001	22.8	28.2	
	6	0	114	124	-1.0	71.1	125.3	11.9	0	1,506	34.2	42.4	
	6	0	24.0	19.0	+5.0	150.2	89.8	12.0	0	1,500	34.1	42.3	

Case 10 Medical History No 39819 Male, aged 19 Height, 162 cm (5 ft 4 in) Weight, 59 kg (130 lbs)	6	0	16 9	20 8	-3 9	105 7	105 7	20 6	0	1,501	25 4	38 5	15 9
	6	0	32 1	27 1	+5 0	200 3	117 7	20 5	0	2,000	33 9	51 3	8 9
	6	0	16 9	19 9	-3 0	105 6	105 7	20 5	71 4	2,000	33 9	51 3	7 5
	6	0	32 1	23 7	+8 4	200 4	117 6	20 9	0	2,001	33 9	51 3	13 2
	6	0	32 1	26 8	+5 3	200 6	117 5	20 7	0	2,000	33 9	51 3	18 8
	6	0	32 1	24 5	+7 6	200 7	117 6	20 5	0	2,001	33 9	51 3	6 0
	9	0	32 1	25 4	+6 7	200 5	117 6	20 5	0	2,000	33 9	51 3	8 2
Case 11 Medical History No 39818 Male, aged 25 Height, 176 cm (5 ft 9 in) Weight, 72 kg (158 lbs)	6	0	11 4	14 4	-3 0	71 3	70 6	12 5	0	1,000	13 9	22 2	
	6	0	24 1	19 5	+4 6	150 3	89 2	13 2	0	1,500	20 8	33 3	
	6	0	24 1	19 0	+5 1	150 6	89 1	13 3	0	1,501	20 8	33 3	13 78
	6	0	24 0	22 1	+1 9	150 1	89 2	13 5	0	1,500	20 8	33 3	17 05
	6	0	24 0	23 4	+0 6	150 2	89 3	13 2	0	1,500	2 08	33 3	10 01
	9	0	24 0	25 3	-1 3	150 2	89 3	13 2	0	1,500	2 08	33 3	9 47
Case 12 Medical History No 39590 Male, aged 26 Height, 167 cm (5 ft 6 in) Weight, 66 kg (145 lbs)	6	0	11 4	15 0	-3 6	71 3	70 5	12 5	0	999	15 1	23 9	
	6	0	11 4	14 3	-2 9	71 2	125 2	12 1	0	1,506	22 8	36 0	
	6	0	24 0	20 0	+4 0	150 1	89 6	12 9	0	1,502	22 8	35 9	
Case 13 Medical History No 39820 Male, aged 33 Height, 169 cm (5 ft 7 in) Weight, 53 kg (117 lbs)	6	0	11 5	10 2	+1 3	71 6	70 6	12 7	0	1,002	18 9	26 1	9 5
	6	0	24 0	19 3	+4 7	150 1	89 6	13 2	0	1,503	28 4	39 1	10 2
Case 14 Medical History No 39182 Male, aged 14 Height, 179 cm (5 ft 10 in) Weight, 42 kg (92 lbs)	6	3 8	11 2	12 7	-1 5	69 7	112 7	9 3	38 7	1,643	39 1	45 3	
	6	26 8	21 6	22 2	-0 6	135 2	76 1	9 9	38 7	1,571	37 5	43 3	

* The articles of food printed in heavy type indicate the addition to the control diet

TABLE 3—SUMMARY OF TABLE 2, GIVING THE AVERAGE DAILY NITROGEN BALANCE IN GRAMS DURING THE DIFFERENT PERIODS OF FEEDING

Case No	Character of Period						
	Control	Protein	Fat	Alcohol	Protein Plus Fat	Fat Plus Alcohol	Protein Plus Alcohol
1	-19	+58	-14	-28			
2	-25	+87	-21	-20			
3	-22		-29	-23	-10		
4	-06	+49	-15	-19			
5	-18	+41	-09	-24		-07	
6	-22	+87	-26	-25	+28		-06
7	-19		+15	-05			
8	-07	+59	-24	-23			
9	-11	+50	-10	-13			
10	-39	+60		-30			
11	-30	+25					
12	-36	+40	-29				
13	+13	+47					
14			.		.	-15	-06

It is evident from a study of these tables that fat and alcohol, when added to a low caloric protein-fat diet, have little or no influence in sparing nitrogen, protein, however, has a very positive influence in this regard. These findings are not absolutely constant in all these observations. Thus, Case 7 has a distinct retention of nitrogen during the high fat feeding and Case 5 (Table 2) exhibits the same phenomenon in the first of the three fat periods, but not in the two subsequent ones. There was no exception to the rule that alcohol was of no value as a nitrogen sparer, even when it was combined with protein, as in Cases 6 and 14, or with fat, as in Cases 5 and 14. With one exception, during a combined fat and protein period in Case 3, there was marked retention of nitrogen when a high protein diet was used, and even in the one instance cited there was a diminished loss of nitrogen, as compared to the control figures.

Lusk,² quoting the work of Thomas and Rubner, shows how the body may maintain nitrogen equilibrium much more readily on a protein-fat diet than on one of protein alone, and how with increasing quantities of fat there is an increasing addition of protein to the body. In the present experiments, the latter statement has proved itself to be

² Lusk, G. The Elements of the Science of Nutrition, Ed 3, 1917, pp 254 and 255

the exception rather than the rule. The results have been so consistent in this regard that the conclusion seems justified that it may be considered to be of no very great value from the point of view of the addition of nitrogen to the body to increase the fat in a protein-fat diet.

Previous investigations, as summarized by Rosemann,³ have yielded substantially the same results with alcohol on mixed diets as the present experiments do on protein-fat diets. The addition of alcohol did not spare nitrogen if given for a period of six days. It may be that if the observations had been continued, protein might have been saved to the body by utilization of alcohol, as was the case in Rosemann's observations. The alcohol, even more constantly than the fat, fails to bring about an assimilation of nitrogen, and is not to be recommended for the dietary of the diabetic if it is desired to spare protein.

The markedly positive nitrogen balances on the "carbohydrate-free diets" with high protein appear to solve the problem of what type of food is best suited to spare protein in the diabetic. The effort produced in these cases may be greater than that seen in normal individuals, inasmuch as most of these patients were either starved or kept on low diets for a considerable length of time before the systematic observations were begun. It has often been noted that it is exceedingly difficult to bring about "a prolonged deposition of protein in the normal adult, when fat is given with it"⁴. In the diabetic, this apparently is not true for six-day periods, at least. Two experiments were conducted in which the high protein feeding was kept up for a longer period in order to illuminate this point. Case 10 (Table 2) was still retaining nitrogen at the rate of 67 gm per day at the end of thirty-three days, Case 11 (Table 2) gave evidence of marked assimilation for twelve days, followed by twelve days in which the nitrogen balance shaded off to terminate in a nitrogen loss in the subsequent period. In summarizing these findings, it may be said that a positive nitrogen balance is readily achieved in diabetes on protein-fat diets with a high protein content, and that such an assimilation of nitrogen may persist for a considerable period before nitrogen equilibrium is reached.

It may be of interest to note in a few of these mild or moderately severe diabetics in whom the acid substances were determined in the urine (Table 2), that none of the food elements, when increased, whether protein, fat or alcohol, had any apparent effect on the amount of the acetone bodies excreted. This is somewhat at variance with the

³ Rosemann, R., in Oppenheimer's *Handbuch der Biochemie des Menschen und der Tiere*, 4, Part 1, p. 436.

⁴ Lusk, G. Loc. cit., Footnote 2, p. 255.

well-known observations that especially the fats may be responsible for an increase of these substances and alcohol for their diminution. It is probable that the very severe diabetic reacts differently in this regard and that, over short periods at least, a high fat diet may result in no increase in the acidosis of moderately severe diabetics.

CONCLUSIONS

The addition of an equal number of calories of protein, fat or alcohol to a low caloric carbohydrate-free diet in cases of diabetes mellitus results in the assimilation of considerable amounts of nitrogen when the protein is used, a favorable nitrogen balance in only occasional instances with fat, and no change in the nitrogen equilibrium when alcohol is given. This would point to a high protein diet as the most advisable low-calory, carbohydrate-free diet by which to conserve the body tissues and furnish a maintenance ration for the diabetic.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

XLIX HUNGER AND APPETITE IN PULMONARY TUBERCULOSIS *

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Recent studies by Carlson¹ and his co-workers emphasize the importance and the relative simplicity of an accurate study of hunger in normal and pathologic conditions. Cannon and Carlson have shown that the sensations of hunger are due to regular periodic contractions of the stomach. Deviations from the normal hunger sensations are associated with changes in the character of the hunger contractions and stomach tonus. This has been demonstrated in man and animals in many conditions such as gastric ulcer, gastric carcinoma, diabetes and gastritis. Meyer and Carlson² studied the condition of hunger and appetite in fever and found that the hunger contractions are absent in temporary fevers when the temperature reaches 103 F and over, and that the dogs will not eat when febrile.

USUAL SYMPTOMS

Loss of appetite and absence of hunger are well recognized clinical manifestations of early and advanced pulmonary tuberculosis. The close relationship between the temperature of the patient and the gastric disturbances in tuberculous patients is well known. Thus, Klebs³ asserts that a patient in advanced pulmonary tuberculosis who may have a good breakfast appetite will by midday and from that time on until the temperature falls again have no desire for food. Stockton⁴ states that tuberculous patients with high temperatures have neither appetite or digestive ability. He also states that gastric dilatation and atony are common in tuberculosis. Conforming to this Klebs states that if the stomach is mapped out in advanced cases dilatation

* Submitted for publication Aug 8, 1918

* From the Tuberculosis Hospital of Cook County Hospital

1 Carlson, A J Control of Hunger in Health and Disease, University of Chicago Press, 1917

2 Meyer, J, and Carlson, A J Contributions to the Physiology of the Stomach XLII—Hunger and Appetite in Fever, Am Jour Physiol, 1917, 44, 222

3 Klebs, A C Tuberculosis, New York, D Appleton & Co, 1909

4 Stockton, C G Diseases of the Stomach, New York, D Appleton & Co, 1914

of the stomach will be found in a large percentage of cases and in some early cases. On the other hand, cases of tuberculosis with persistent temperature are readily relieved of this temperature elevation by correction of the gastric complaint.

THE PRESENT WORK

The present study was conducted on six patients with early, moderately advanced, and far advanced pulmonary tuberculosis. None of the patients showed signs of peritoneal or intestinal involvement or had any gastric complaint other than loss of appetite. These precautions were taken because it is well known that lesions of the peritoneum, intestine or stomach exert an inhibitory influence on gastric contractions.

The method pursued was briefly as follows. The patients were carefully examined after a clinical diagnosis of pulmonary tuberculosis was made, this being confirmed by routine sputum analysis and roentgen-ray examination. The temperature was recorded and the patient observed for a period of four to seven days before any work was commenced. In general, the cases selected were those showing a temperature of from 100 to 101 F at some time during the day. On the day before the kymograph tracing was taken the patient was given his supper at 4 p. m. and nothing thereafter. The experiment was started at 8 a. m. the following morning, so that the starvation period was about sixteen hours. In order to obtain a record coincident with the afternoon rise in temperature a number of experiments were begun at 11 a. m. Patients have no difficulty in swallowing the balloon after one or two attempts. The great difficulty is to obtain from the patient an expression of his sensations with the hunger contractions. The patients in the Cook County Hospital are foreigners for the most part, and it is not only difficult to explain to them what is desired but even more difficult to obtain an intelligent response to questions.

REPORT OF CASES

CASE 1—History—Anton A., Greek laborer, aged 23, complained of cough, pain in the chest, chilly sensations, fever and loss of appetite. The details of the history are unimportant.

Examination—The physical findings were dulness over the left apex, fine râles and bronchovesicular breathing, flatness beginning at the level of the eighth dorsal vertebra, with diminished vocal and breath sounds. Traube's space was absent. There were scattered râles in the right apex and a pleuritic friction rub on the right. The sputum contained tubercle bacilli. The roentgen-ray report by Dr. Turley was "The left apex is blocked out, pleurisy with effusion, right costodiaphragmatic angle is also obliterated."

Temperature Record—From the date of entrance, Feb. 12, 1918, until the first day of the experiment on February 19, the average morning temperature was 96.6 F. The afternoon temperature was 99.4.

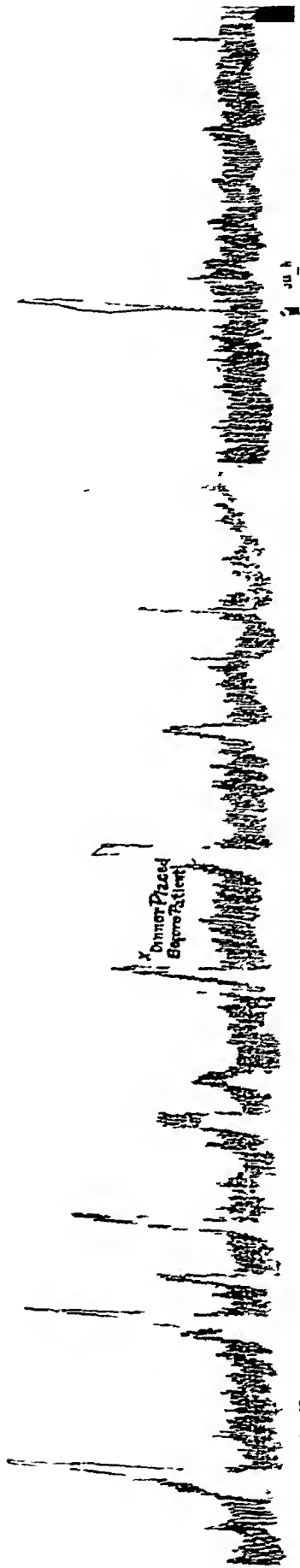


Fig 1 (Case 1) —Normal hunger contractions in an early case of pulmonary tuberculosis Subnormal temperature At 1 food was placed before the patient, but he was not allowed to eat

Observation of February 19—A record of the stomach contraction was taken, preceded by a fast of sixteen hours. The record was taken from 8 a. m. until 12 m. The temperature during this period was 99 F. Contractions began about one-half hour after swallowing the balloon. They were normal and regular. The patient did not experience the contractions as such. When asked whether he felt hunger he did not seem to understand. He was told to squeeze the finger of the observer whenever he experienced discomfort or hunger pang. He failed to do this, and the experiment was discontinued at noon. He readily ate the dinner which was then offered him.

Second Observation—Three days later, with the patient's temperature at 99 F, another record was taken, beginning at 11 a. m., allowing a starvation period of nineteen hours. The latent period before the stomach assumed any tonus was approximately one hour. Regular hunger contractions then appeared. The patient was then asked whether he felt hungry, but could give no intelligible response. In the midst of a period of hunger contractions food was placed before him, but he was not allowed to eat it. Figure 1 shows the gradual inhibition of hunger contractions at the sight of food.

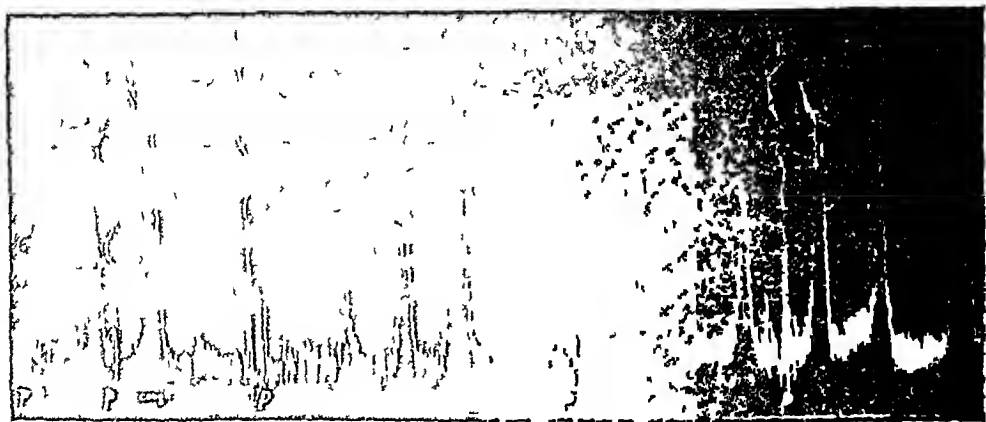


Fig 2 (Case 2)—Vigorous contractions in an advanced case of pulmonary tuberculosis with marked cachexia, emaciation and septic temperature. Some of the contractions are incompletely recorded because they were so intense as to force the writing point out of the manometer.

CASE 2—History—Anton K., Greek, aged 29, complained of having a cough for fifteen years. In the past two months he began to feel much weaker and complained of loss of appetite, loss of weight and night sweats.

Examination—Physical findings were those of a cavity in the left upper lobe and complete involvement of the right lung. Fluoroscopic examination disclosed the presence of the cavity with a generalized pulmonary tuberculosis. The sputum contained numerous tubercle bacilli.

Temperature Record—The temperature was characteristic of an advanced ulcerative type with subnormal temperature in the morning, rising to 102 and 103 F in the afternoon.

Observation of February 25—The usual period of fast was observed. The temperature of the patient during the observation ranged from 99.8 to 101 F. Hunger contractions began almost immediately after swallowing the balloon. They were vigorous, continued for an hour and were followed by a period of quiescence. The next period was characterized by more vigorous contractions than previously. With each contraction (Fig 2) the patient became extremely restless, cried and pointed to his abdomen. When asked whether he was hungry or felt hunger, he cried and pointed to his epigastrium as if he were in pain. The patient died on March 4.

CASES 3 AND 4—*History*—These patients presented the same clinical picture as Case 2, and therefore the details of their findings are not here reported. The temperature records of these three patients were essentially alike, and death occurred in all three cases.

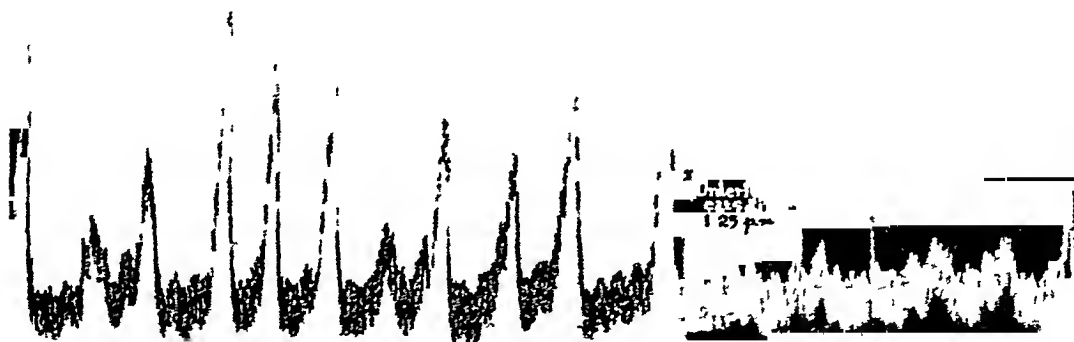


Fig 3 (Case 3)—Vigorous contractions of another case of advanced pulmonary tuberculosis. At 1 the orderly ate his own meal in the presence of the patient. Compare also the effect in Figure 1.

Observation of March 11—The temperature was 101 F. Contractions commenced immediately and were regular, periodic and extremely vigorous, lasting four hours. The patient could not say that he was hungry. At 1 30 p. m. the orderly of the ward brought his own meal into the room and ate it with the patient looking on. The hunger contractions almost immediately stopped (Fig 3). Stomach tonus reappeared in fifteen minutes, followed again by vigorous contractions. At 2 p. m. a visiting physician entered the room, and again there was an immediate cessation of contractions.



Fig 4 (Case 4)—Entire absence of contractions in another advanced case. Temperature 102 F.

CASE 4—*Observations of February 26*—Temperature was 102 F. The usual period of fast was observed. After inflating the balloon in the stomach a few initial contractions occurred. These gradually disappeared, and for a period of one and three-quarter hours there were no contractions, nor any evidence of stomach tonus (Fig 4). The patient vomited the balloon at the end of two hours, which necessitated repetition of inflation, and again contractions were present for a short time, followed by complete cessation. The temperature at the end of the period was 101.6. When asked if he desired food, he said he did not care. Food was placed before him, and he ate only a part of it.

Observation of February 27—This revealed intense contractions so vigorous that the writing point was forced out of the manometer.

CASE 5—History—The patient, Harry W, presented a case of moderately advanced tuberculosis. He complained of cough, expectoration and shortness of breath. He volunteered that he would begin a meal thinking that he was hungry, eat a small part of it and leave it.

Examination—The physical findings were those of dulness over the apex, bronchovesicular breathing and fine, scattered, crepitant râles bilaterally. The sputum was positive, and the roentgen ray revealed a generalized mottling with failure of the apices to light up.

Temperature Record—This ranged from 97 to 101 and from 99 to 102 F.

Observation of February 21—This began at 8 a. m. after a starvation period of sixteen hours. The stomach tonus was low, and the patient was very nervous. The temperature was 100 F.

Observation of March 1 after a starvation period of nineteen hours with temperature ranging from 99 to 101 during the tracing. At first there was a series of normal hunger contractions, followed by vigorous contractions felt as such and referred to the stomach. As the orderly ate his own dinner in full view of the patient, the contractions were only somewhat diminished to recur with still greater vigor (Fig 5).

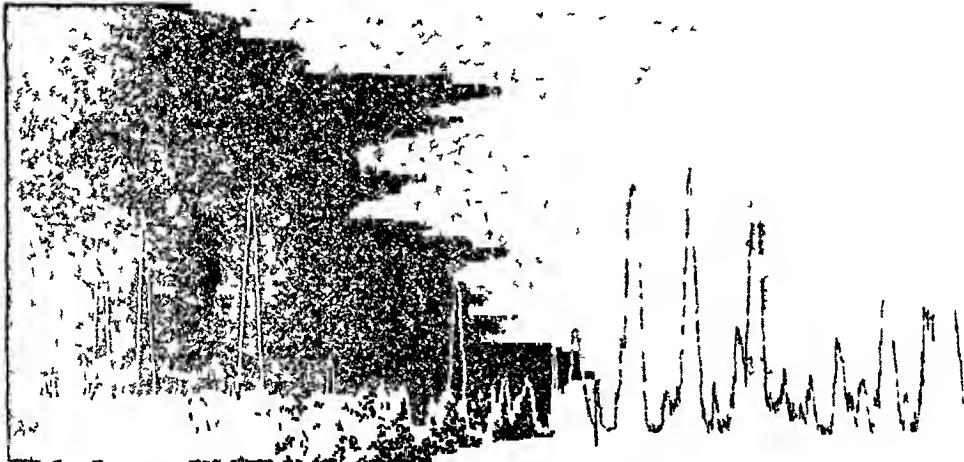


Fig 5 (Case 5)—Normal contractions in a moderately advanced case with low-grade chronic temperature from 99 to 100.

CASE 6—History—The patient, Edward M, had a case of moderately advanced tuberculosis.

Observation—This was taken with the temperature about 101 F. The contractions were only of moderate intensity, but nevertheless the patient stated that he felt something and said that he was hungry. At one point with no contractions he said he had an appetite and asked for whisky. This was promised, but not given. Stomach tonus continued, and one half hour later contractions appeared.

DISCUSSION OF RESULTS

The outstanding fact in all these observations is that contractions and stomach tonus are present. Case 1 presents an almost typical normal hunger contraction record. It is surprising to find in Cases 2, 3 and 4 such vigorous gastric contractions in view of the extreme cachexia, emaciation and advanced stage of the tuberculous process. Judging from the old clinical view, instead of an active stomach we

should expect dilatation and atony in advanced tuberculosis. The present observation in these patients of increased tonus and contractions accords with the observation of Luckhardt,⁵ who noted increased hunger contractions in cases of cachexia associated with diabetic mellitus in man and in the cachexia of mangy dogs. The temperature of 101 F apparently does not affect the hunger mechanism. In Case 4, however, with the temperature at 102 there is complete atony of the stomach and entire absence of the hunger contractions. This is also in accord with previous observations in animals. Cases 5 and 6 again point to the fact that patients with a low type of temperature persisting over a long period of time and with evident signs of intoxication present normal hunger contractions and stomach tonus.

COMMENT

The association in these cases of hunger contractions with absence of hunger sensations suggests the possibility that these contractions are probably not registered in consciousness as such. Again, in these cases the personal factor must be considered. Hunger contractions are present in some individuals, but instead of being recognized by the patient as such they are described as restlessness, headache and other symptoms. Again Carlson has recently shown that in long continued fasts hunger contractions are present, but are not recognized as such. This may be the case in chronic fevers, in which cases the hunger contractions are present.

5 Luckhardt, S. Contributions to the Physiology of the Stomach—XI—The Cause of Polyphagia in Pancreatic Diabetes, *Am Jour Physiol*, 1914, **33**, p. 313.

THE ELECTROCARDIOGRAM IN THYROID DISEASE^{*}

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The effect of thyroid disease on the heart, and especially on the electrocardiogram, has been followed in the present investigation chiefly from two points of view. In twenty-three cases we have compared the severity of the disease, as shown by the variation of the total metabolism from the normal, with the amplitude of the T-wave in the electrocardiogram. In the second place, in forty-seven cases of hyperthyroidism we have determined the frequency and type of arrhythmia. Also heart rates, blood pressures and electrocardiographic evidence of left ventricular preponderance and of general muscular tremor have been of interest. The basal metabolism was determined by means of the Benedict Unit apparatus¹. The electrocardiograms were taken with the Cambridge Model of the Einthoven string galvanometer and carefully standardized.

It has been said that the T-wave is high in hyperthyroidism and low, absent, or even inverted in hypothyroidism. In our series of cases there has been little if any parallelism between the basal metabolism and the amplitude of the T-wave in comparing different cases, but in individual cases, especially those with hypothyroidism with variations in the basal metabolism, there may occur corresponding changes in the height of the T-wave (see the accompanying table). In hypothyroidism the T-wave is low and increases under treatment. In hyperthyroidism it is also often low and its height does not parallel necessarily changes in the height of the metabolism, it sometimes runs conversely to it. In two of the patients suffering from auricular fibrillation while under treatment with digitalis, this drug had much more effect on the T-wave (flattening it) than had any differences of basal metabolism which these same patients showed.

Three of our forty-seven cases had paroxysms of auricular fibrillation, three had apparently permanent auricular fibrillation, one had paroxysms of auricular flutter with the normal rhythm interrupted by auricular premature contractions, while a number of others showed premature contractions.

^{*} Submitted for publication June 22, 1918.

^{*} From the Medical Clinic of the Massachusetts General Hospital.

¹ Means, J H, and Aub, J C. Jour Am Med Assn, 1917, 69, 33.

TABLE SHOWING VARIATIONS IN T-WAVE

Case	Sex	Total Metabolism		Electrocardiograms		
		Date	Percentage Variation from the Normal	Date	T(10-4 Volts)	Pulse Rate
C A (Case of complete heart-block First seen while taking large doses of thyroid gland. This drug was stopped 11/16/16)	♀	11/13/16	-41	11/13/16	-2	Δ=auricular rate
		11/18/16	+40	11/18/16	-1	A=120
		11/20/16	+28	11/20/16	-1½	A=100
		12/ 4/16	+ 3	12/ 4/16	-1½	A=100
		12/17/16	+14	12/23/16	+2	A= 75
						A= 78
		1/28/17	+ 8	1/31/17	+0	A= 95
M T P	♀	11/ 7/16	+58	11/ 8/16	+1½	106
		2/28/17	+53	2/28/17	+2½	140
		4/18/17	+46	4/18/17	+1½	120
M M	♀	2/12/17	+74	2/ 7/17	+ ½	110
		3/27/17	+79	4/ 9/17	+2	108
				Partial thyroidectomy 4/16/17		
		4/29/17	+15	5/ 2/17	+3½	76
K L	♀	2/ 8/17	+26	2/ 7/17	+2	110
		4/28/17	+28	4/28/17	+2	110
V D	♀	2/15/17	+28	2/12/17	+4	120
		4/ 5/17	+27	4/ 5/17	-3	118
A B	♀	2/18/17	+37	2/ 8/17	+3	135
				Thyroidectomy right lobe and ½ left lobe 2/14/17		
		3/28/17	+ 4	3/28/17	+1½	110
M H	♀	2/17/17	-47	2/19/17	+1½	90
		3/ 7/17	+27	3/ 8/17	+3	100
B M T	♀	3/12/17	+39	3/13/17	+5	150
		4/29/17	-47	4/16/17	+4	124
M T	♀	3/13/17	+64	3/13/17	+3	180
				Thyroidectomy right lobe and isthmus 3/27/17		
		4/ 1/17	+85	4/ 2/17	+2½	105
E M	♀	11/19/16	+34	11/16/16	0	120
		4/ 9/17	+ 1	4/ 9/17	- ½	105
E S	♀	10/ 7/15	+73	10/ 5/15	-4	100
		3/28/17	+87	3/28/17	+4½	120
C M	♀	3/29/17	+84	3/26/17	+3	120
		4/ 6/17	+67	4/ 9/17	+1½	107
J B	♀	2/17/17	+37	2/19/17	-3	75
T W	♀	4/17/15	+49	4/10/15	+2	85
A L	♀	5/ 2/17	+63	5/ 2/17	-2	110
C J	♂	4/ 3/17	+48	4/ 3/17	-3	110
P B K	♀	4/10/17	+60	4/11/17	+2	124
E H	♀	6/ 5/17	+44	6/ 5/17	+3	80
T D	♂	3/12/17	+29	3/ 9/17	-1½	135
C M (Paroxysmal auricular fibrillation)	♀	12/20/16	-74	12/20/16	0	160
						(auricular fibrillation)
		1/ 9/17	-34	1/10/17	-4	108
					(digitalis effect)	(normal rhythm)
		2/ 1/17	-58	2/ 7/17	-2	122
						(normal rhythm)
		4, 24/17	+73	4/24/17	-3	137
						(normal rhythm)

TABLE SHOWING VARIATIONS IN T-WAVE—(Continued)

Case	Sex	Total Metabolism		Electrocardiograms		
		Date	Percentage Variation from the Normal	Date	T(10 ⁻⁴ Volts)	Pulse Rate
E T B (Paroxysmal auricular fibrillation)	♂	2/ 3/17	+71	2/ 5/17	—2	115 (normal rhythm)
		2/16/17	+61	2/18/17	—2	145 (auricular fibrillation)
		2/25/17	+69	2/23/17	—6 (digitalis effect)	108 (auricular fibrillation)
		(Thyroidectomy, right lobe and isthmus, 3/5/17)				
		3/14/17	+34	3/13/17	—4½	90 (normal rhythm)
		4/ 7/17	+67	4/ 7/17	—1	126 (normal rhythm)
E R	♀	11/14/14	—25	11/12/14	0	82
		11/23/14	—15	11/23/14	1½	87
		(After 24 grams of thyroid gland extract in 8 days)				
H L (Under treatment for cretinism)	♀	2/14/17	—17	2/14/17	—2½	98
		3/ 7/17	+ 5	3/ 7/17	0	105
		3/16/17	+ 1	3/14/17	+1	112
		4/24/17	+20	4/24/17	+2	120

The degree of tachycardia paralleled the basal metabolism percentage but moderately. In one unusual case of complete heart block (C A in the table) the ventricular rate showed but a few beats change between the time of hyperthyroidism and the time of normal basal metabolism. In this case, however, as reported in a previous paper,² the auricular rate as shown electrocardiographically varied with the basal metabolism, 120 per minute at +42.5 per cent and 75 per minute at +3 per cent.

Left ventricular preponderance was found by the electrocardiogram in only three of twenty-seven of hyperthyroidism. The index of preponderance in these cases was from +26 to +30. The normal borderline of this index is from +20 to +30 as described in a previous paper.³ Variable hypertension was frequently present with figures of 150 to 200 mm mercury systolic and 90 to 110 mm diastolic. In one case the pressure dropped within a few weeks from 210 mm to 130 mm systolic and from 100 mm to 75 mm diastolic, while the basal metabolism decreased from +47 per cent to +27 per cent, in this case the T-wave rose in amplitude from 0.15 to 0.28 millivolt. General muscular tremors shown electrocardiographically are common in hyperthyroidism.

2 Aub, J C, and Stern, N S. THE ARCHIVES INT MED, 1918, **21**, 130

3 White, P D, and Bock, Am Jour Med Sc, 1918, **156**, 17

SUMMARY

Very limited parallelism has been found between the basal metabolism and the amplitude of the electrocardiographic T-wave in a series of twenty-seven cases of thyroid disease

Auricular fibrillation, including the paroxysmal type, is not uncommon in hyperthyroidism as shown in our series by six out of forty-seven cases of hyperthyroidism (13 per cent) Paroxysmal auricular flutter has been seen in one of our cases

Tachycardia, frequent hypertension and frequent tremor while at rest occurred in the cases of hyperthyroidism although not always parallel to the total metabolism

RENAL FUNCTION AS MEASURED BY THE ELIMINATION OF FLUIDS, SALT AND NITROGEN, AND THE SPECIFIC GRAVITY OF THE URINE

II THE EFFECT OF HIGH, LOW AND NORMAL DIETS^{*}

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Since Hedinger and Schlager¹ introduced the method of testing renal function by measuring the volume and the specific gravity and estimating the sodium chlorid output in two-hourly specimens of urine throughout the day and in a single specimen during the night, it has received general acceptance in this country. In conducting the test, much stress was laid on the fact that the diet necessary to produce satisfactory results must contain a considerable quantity of the diuretic substances ordinarily found in the food, such as fluids, salts and purins. Two forms of diets have been used fairly extensively, the one consisting of three meals,² the other of five.³ The results obtained in both appear to be very similar. In order to obtain a clear understanding of this method of testing renal function, it was necessary to formulate precisely what the normal reaction was. This was attempted.⁴ Since that report was made, a large number of normal tests have been carried out, and in the light of these it becomes apparent that the former standards are wrong in some respects and should be corrected. The question as to what diet should be used in carrying out this test is a far-reaching one. If the diet need not be limited in any way, there is a wider field of usefulness for the test, especially in general practice. In the present paper, the attempt will be made to define as closely as possible the normal results of this method of analyzing the urine on various diets and to note the value of widely divergent diets in cases with impaired renal function.

FORMS OF DIETS

The diets employed were three: a high protein diet, a low protein diet, and a normal diet. The *high protein diet* was the one originally advocated for the performance of the test.² It contains about the amount of protein that a normal individual with a good appetite will consume. The designation "high protein diet" may, therefore, be a misnomer. However, it is so designated to indicate the contrast with

^{*} Submitted for publication May 23, 1918

^{*} From the Medical Clinic of The Johns Hopkins Hospital

1 Hedinger and Schlager. *Deutsch Arch f klin Med*, 1914, **114**, 120

2 Mosenthal, H O. *THE ARCHIVES INT MED*, 1915, **16**, 733

3 O'Hare, J P. *THE ARCHIVES INT MED*, 1916, **17**, 711

4 Mosenthal, H O, and Lewis, D S. *Jour Am Med Assn*, 1916, **67**, 933

the other diets This diet contains approximately 1,760 c c of fluid, 85 gm of salt and 134 gm of nitrogen, and considerable quantities of purin substances in the soup, meat, tea and coffee The *low protein diet* was that in use at this hospital It was found that when no restrictions were placed on the persons taking this diet, protein equivalent to from 3 to 4 gm of nitrogen was usually consumed in the twenty-four hours This was deemed sufficiently low for the purposes of the present observations The diet contained no tea or coffee or purins in any form Some alcohol was allowed as sherry This was given in less than one-half of the cases studied The remainder of the food consisted largely of starches, which have a marked effect in preserving the body protein and thereby limiting the amount of waste products to be excreted in the urine The *normal diet* consisted of the food which the subject chose The aim was to determine whether it was possible to allow a person to continue his normal dietary habits while the test was carried out In the remainder of this article these diets will be spoken of respectively as the high, the low, or the normal diet

The only other restrictions placed on the persons tested were that no food or fluid should be taken between meals, and that the collection of the night specimens should begin three hours after supper The specimens were usually collected at two-hourly intervals from 8 a m to 8 p m If supper were taken after 5 p m, the collection of the night specimen was begun at a correspondingly later time It may be that it is not necessary to limit the frequency with which fluid and food are taken, however, it did not seem advisable to attempt too much at one time, and it was deemed best not to extend the variations too much so that clear-cut results might be obtained

The specific gravity of the urine was measured at room temperature by reliable floats, the nitrogen was determined by the Kjeldahl process and the sodium chlorid by the method of Volhard The normal persons tested were men and women of the teaching staff and student body

THE NORMAL STANDARD

The normal standard as advocated previously was as follows A maximum specific gravity of 1.018 or higher, a variation of 9 degrees or more between the minimum and maximum specific gravity readings, and a night urine of 400 c c or less, with a specific gravity of 1.018 or over and a concentration of nitrogen of at least 1 per cent (Table 1)

* *Breakfast* Sherry (30 c c), baked apple, stewed prunes, orange, hominy cornstarch ($\frac{2}{3}$ hominy $\frac{1}{3}$ cornstarch) cereal cream (15 c c) sugar, butter

Dinner Sherry (30 c c) potato, baked or mashed, string-beans cabbage, carrots, lettuce, onions, tomatoes, cucumber pickles fruit cornstarch pudding fruit tapioca pudding, sugar, butter

Supper As dinner

At the time these criteria were formulated, it was not realized how profoundly the activity of the kidney may be affected by many influences. Nervous tension, very hot or cold weather, and what may be termed the "renal habits" of any person, all have appeared to play a distinct rôle in causing differences to appear that were not at first appreciated. Lyle and Sharlit⁵ have called attention to the fact that the night urines in normal persons may exceed 400 c c by a considerable margin and that the variations in the specific gravity may be less than 9 and that there are instances in which the concentration of nitrogen in the night urine is less than 1 per cent. The results of Lyle and Sharlit in regard to the fixation of the specific gravity are probably somewhat exaggerated as they obtained them when the subjects were kept for several days on a diet constant in fluids as well as solids. This introduces a new factor for which due allowance must be made. The same phenomenon may be noted in the observations to be recorded in this communication, but not to the same degree. The presence of larger amounts than 400 c c in the night urine and a concentration of nitrogen of less than 1 per cent in the night urine has been a rather common finding in the present series of normals.

TABLE 1—RESULTS OF A TEST MEAL FOR RENAL FUNCTION IN A NORMAL PERSON. THIS TABLE SHOWS AT WHAT INTERVALS THE URINE WAS COLLECTED. IT MEETS ALL THE REQUIREMENTS WHICH WERE FORMERLY REGARDED AS CHARACTERISTIC OF A NORMAL TEST.

Time of Day	C C	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	Grams	Per Cent	Grams
8 10	315	1 006				
10 12	128	1 014				
12 2	120	1 017				
2 4	122	1 020				
4 6	76	1 022				
6 8	100	1 027				
Total, Day	861		0 78	6 71	0 79	6 80
Night, 8-8	248	1 025	0 69	1 71	1 23	3 05
Total, 24 Hours	1,109			8 42		9 85
Intake	1,760			8 50		13 40
Balance	+651			+0 08		+3 55

Table 1 may serve to recall what determinations are carried out and how a test meal for renal function is recorded. In the interpretation of this procedure as a means of measuring renal activity, certain points, the maximum specific gravity, the variation in specific gravity, the quantity of the night urine and its specific gravity and concentra-

⁵ Lyle, W G, and Sharlit, H. THE ARCHIVES INT MED, 1918, **21**, 366

tion of nitrogen have been emphasized There are probably other features that deserve to be considered in this connection, however, thus far there are no observations that have laid any stress on them In Tables 2, 3, 4 and 5, in order to save space, only a summary of what

TABLE 2—SUMMARY OF RESULTS OF THE COLLECTION OF URINARY SPECIMENS AT TWO-HOURLY INTERVALS DURING THE DAY AND FOR A TWELVE-HOUR PERIOD AT NIGHT IN NORMAL PERSONS WHILE ON THE "HIGH" DIET

Date	Day of Diet	Specific Gravity*				Night Urine	
		Highest	Lowest	Degrees Variation	Night Urine	Nitrogen, Per Cent	Volume, C O
6/27/17	1	34	30	4	34	2 70	160
6/11/15	1	33	24	9	29	1 85	213
5/ 9/17	2	33	05	28	31	1 63	175
6/19/17	1	30	05	25	25	1 19	294
6/27/17	1	29	13	16	29		.
11/21/17	1	29	07	22	23		258
5/19/17	2	28	07	21	14	0 61	326
5/18/17	1	28	03	25	21	1 25	170
2/10/14	3	28	03	20	23	1 30	374
11/22/17	2	27	03	19	15		425
5/18/17	1	27	03	24	26	1 48	169
6/10/15	1	27	06	21	25	1 23	243
11/22/17	2	27	03	19	18		456
11/22/17	2	27	09	18	19	1 28	334
6/19/17	1	25	15	10	15	0 87	503
2/14/16	2	25	07	18	25	1 53	240
1/17/16	1	24	09	15	23	1 43	350
5/18/17	1	22	05	17	03	0 56	417
5/19/17	2	22	06	16	09	0 54	539
1/17/16	1	21	03	13	21	1 19	350
2/14/16	1	21	07	14	19	0 95	400
12/11/14	3	20	10	10	20	1 23	375
12/12/14	1	20	07	13	18	0 76	563
2/10/17	3	20	09	11	13	0 74	615
6/ 3/15	1	19	07	12	19	1 14	355
4/15/15	1	19	07	12	17	1 20	352
11/21/17	1	19	07	12	19		280
4/ 6/15	1	19	09	10	19	1 12	330
2/10/17	1	19	06	13	13	0 62	721
12/ 5/14	2	18	03	10	18	1 03	402
6/ 3/15	1	18	03	10	18	1 03	390
11/ 2/17	1	14	03	6	13		650

* Last two figures only

may be considered the salient features of test meals for renal function, as carried out in normal subjects, while on high, low or normal diets, is given

TABLE 3—SUMMARY OF THE RESULTS OF THE COLLECTION OF URINARY SPECIMENS AT TWO-HOURLY INTERVALS DURING THE DAY AND FOR A TWELVE-HOUR PERIOD AT NIGHT IN NORMAL PERSONS WHILE ON THE "LOW" DIET

Date	Day of Diet	Specific Gravity*				Night Urine	
		Highest	Lowest	Degrees Variation	Night Urine	Nitrogen, Per Cent	Volume, C C
11/23/17	1	36	12	24	12	0.47	565
6/28/17	1	34	13	21	20	1.44	260
11/23/17	2	30	13	17	13		525
11/23/17	1	30	07	23	18		104
6/16/17	2	30	07	23	12	0.45	475
1/10/16	3	29	06	23	20	1.14	215
6/29/17	2	29	05	24	19	1.26	197
11/24/17	2	28	12	16	12		408
2/15/16	1	28	16	12	27	0.40	210
6/16/17	2	28	05	23	11	0.62	391
1/20/16	3	27	12	15	27	1.57	178
2/15/16	1	27	10	17	25	1.41	267
11/23/17	1	26	06	20	20		174
11/24/17	2	26	09	17	13		554
1/18/16	1	26	06	20	26	1.24	195
6/29/17	2	25	03	22	25	1.41	188
1/19/16	2	25	06	19	25	1.29	210
6/28/17	1	25	05	20	20	0.95	340
2/7/17	3	25	06	19	15	0.74	429
6/21/17	2	25	05	20	13	0.84	315
2/7/17	1	25	10	15	25	1.30	210
2/16/16	2	24	09	15	24	0.83	240
6/20/17	1	24	11	13	19	1.38	167
5/16/17	1	24	02	22	15	0.87	280
2/17/16	3	23	14	9	23	0.66	90
2/7/17	3	23	07	16	13	0.23	523
1/19/16	2	23	07	16	23		250
1/18/16	1	22	06	16	22	1.23	200
5/16/17	1	22	03	19	11	0.52	489
5/17/17	2	21	03	18	09	0.31	637
2/16/16	2	21	06	15	21	0.74	300
2/17/16	3	21	12	9	20	0.69	255
5/16/17	1	20	03	17	09	0.46	512

* Last two figures only

TABLE 4—SUMMARY OF RESULTS OF THE COLLECTION OF URINARY SPECIMENS AT TWO-HOURLY INTERVALS DURING THE DAY, AND FOR A TWELVE-HOUR PERIOD AT NIGHT IN NORMAL PERSONS WHILE ON THEIR CUSTOMARY "NORMAL" DIETS

Date	Specific Gravity*				Night Urine	
	Highest	Lowest	Degrees Variation	Night Urine	Nitrogen, Per Cent	Volume, C C
6/18/17	37	20	17	26	1.73	331
11/20/17	36	16	20	16		660
7/ 9/16	33	25	8	31		100
10/23/16	33	15	18	15		568
10/24/16	32	18	14	25		370
7/ 8/16	31	23	8	31		210
6/11/16	31	14	17	30	2.05	340
10/18/16	31	20	11	31		94
6/26/17	31	16	15	27	1.84	221
6/26/17	30	25	5	30		275
5/15/17	30	09	21	22	1.40	369
5/ 9/16	30	19	11	20	1.31	350
10/29/14	30	26	4	27	2.07	290
3/18/16	30	21	9	30	2.26	240
3/23/16	30	10	20	30	1.63	250
7/11/16	30	09	21	29		185
7/21/16	30	18	12	25		186
10/23/16	30	26	4	26		260
10/18/16	30	13	17	16		750
5/15/16	30	12	18	12	0.85	440
10/23/16	30	24	6	24		500
11/20/17	30	07	23	28	1.32	266
6/21/17	29	18	11	24		373
7/20/16	29	19	10	25		195
7/10/16	29	22	7	24		235
11/20/16	29	14	15	20		645
10/25/16	29	19	10	22		422
7/12/16	28	22	6	28		198
10/20/16	28	21	7	28		270
10/25/16	28	20	8	28		268
10/19/16	28	10	18	28		300
10/19/16	28	12	16	28		226
11/19/17	28	08	20	17		398
7/17/16	27	20	7	27		222
6/10/16	27	16	11	27	1.61	330

TABLE 4—(Continued)

Date	Specific Gravity*				Night Urine	
	Highest	Lowest	Degrees Variation	Night Urine	Nitrogen, Per Cent	Volume, C O
7/10/16	26	12	14	28		165
7/16/16	26	13	13	26		210
11/19/16	26	10	16	26		395
6/10/16	26	14	12	21		330
10/18/16	26	13	13	20		330
10/26/16	26	10	16	21		305
11/19/16	26	12	14	21		250
5/14/17	25	12	13	15	0 87	457
6/20/17	25	17	8	19		430
7/22/16	25	10	15	25		170
7/ 9/16	25	04	21	17		255
6/ 9/16	25	13	12	17	1 08	735
10/19/16	25	09	16	15		536
10/25/16	25	18	7	22		525
10/18/16	25	15	10	19		312
10/18/16	25	08	17	21		375
10/24/16	25	13	12	24		530
10/26/16	25	19	6	25		510
10/30/17	25	05	20	18	1 43	361
10/19/16	24	22	2	22		506
5/15/17	23	03	20	14	0 85	443
3/23/17	23	07	16	22	1 46	475
7/15/16	23	03	20	15		180
10/19/16	23	09	14	16		395

* Last two figures only

TABLE 5—SUMMARY OF SALIENT FACTS ON THE UPINARY SPECIMENS COLLECTED DURING PERIODS OF "HIGH," "LOW," AND "NORMAL" DIETS IN NORMAL PERSONS

	Number of Observations		
	"High" Diet	"Low" Diet	"Normal" Diet
Maximal specific gravity			
20 or higher	4	5	22
20 to 25	12	16	22
24 to 20	8	12	5
19 or 18	7	0	0
Less than 18	1	0	0
Total number of observations	32	33	59
Degrees of variation of specific gravity			
13 or over	20	26	22
12 to 9	10	7	12
8 to 5	1	0	12
4 or less	1	0	2
Total number of observations	32	33	59
Specific gravity of night urine			
21 or over	12	12	41
20 to 18	10	7	6
17 to 15	3	2	10
14 to 10	4	9	2
Less than 10	2	2	0
Total number of observations	32	23	59
Volume c c of night urine			
400 or less	21	23	42
401 to 500	4	4	7
501 to 600	2	5	6
601 to 700	2	1	2
701 to 750	1	0	2
Total number of observations	31	33	59
Nitrogen per cent in night urine			
1% or higher	18	11	13
0.99% to 0.89%	2	5	3
0.79% or less	6	11	0
Total number of observations	26	27	16

In Tables 2, 3 and 4 the results of the tests for renal function are given for the high, low and normal diets. They are arranged in order from those with the highest maximum specific gravity to those with the lowest. The dates on which the tests were made are included because they indicate that all seasonal variations, especially as far as temperature is concerned, are taken into consideration. The number of days on which an individual was on a given diet are recorded, as this may naturally have some bearing on the result.

THE MAXIMAL SPECIFIC GRAVITY IN NORMAL TESTS

The last test noted in Table 2 on the high diet is remarkable. It is the only example in the tests (including those of Tables 3 and 4 on the low and normal diets) in which the maximum specific gravity was lower than 1.018. This may be a faulty observation, or it may be a phenomenon of rare occurrence. This person's other test meals, five in number, all yielded specific gravities comparable with other normals, and her phenolsulphonephthalein excretion, blood urea and total non-protein nitrogen and Ambard's constant were strictly within normal limits. Taking all the tests (124 in number, Table 5) into consideration, it is apparent that such a low maximum specific gravity is likely to be found in less than 1 per cent. of normal persons, and may be disregarded. It is probably due to some anomalous water excretion, which occurs very rarely.

In the other tests it was found that the maximum specific gravity was always 1.018 or higher on the high diet, and 1.020 or over on the low or normal diets. Evidently, this is one of the most constant features to be relied on in estimating normal renal function by the test meal procedure. This may possibly be more forcibly demonstrated in Chart 1. Here it may be noted how in general the quantity of salt and nitrogen excreted varied according to the diet, and yet the fluctuations in the specific gravity reached a maximum of at least 1.018 on the high diet and 1.020 on the low or normal diets on each day.

In order to obtain a more complete knowledge of the reasons for a certain maximal concentration in the various specimens of this method of collecting urines, as well as for the other phenomena to be taken up in detail subsequently, it was decided to give a diet whose influence on the kidney should be as nearly uniform as possible. This was accomplished by means of starvation. A constant quantity of water was given at two-hourly intervals, at the time when the period for each day specimen was begun. This was successfully carried out in five experiments, in two others, the water was taken in varying amounts and in one the quantity of water drunk was not noted. The

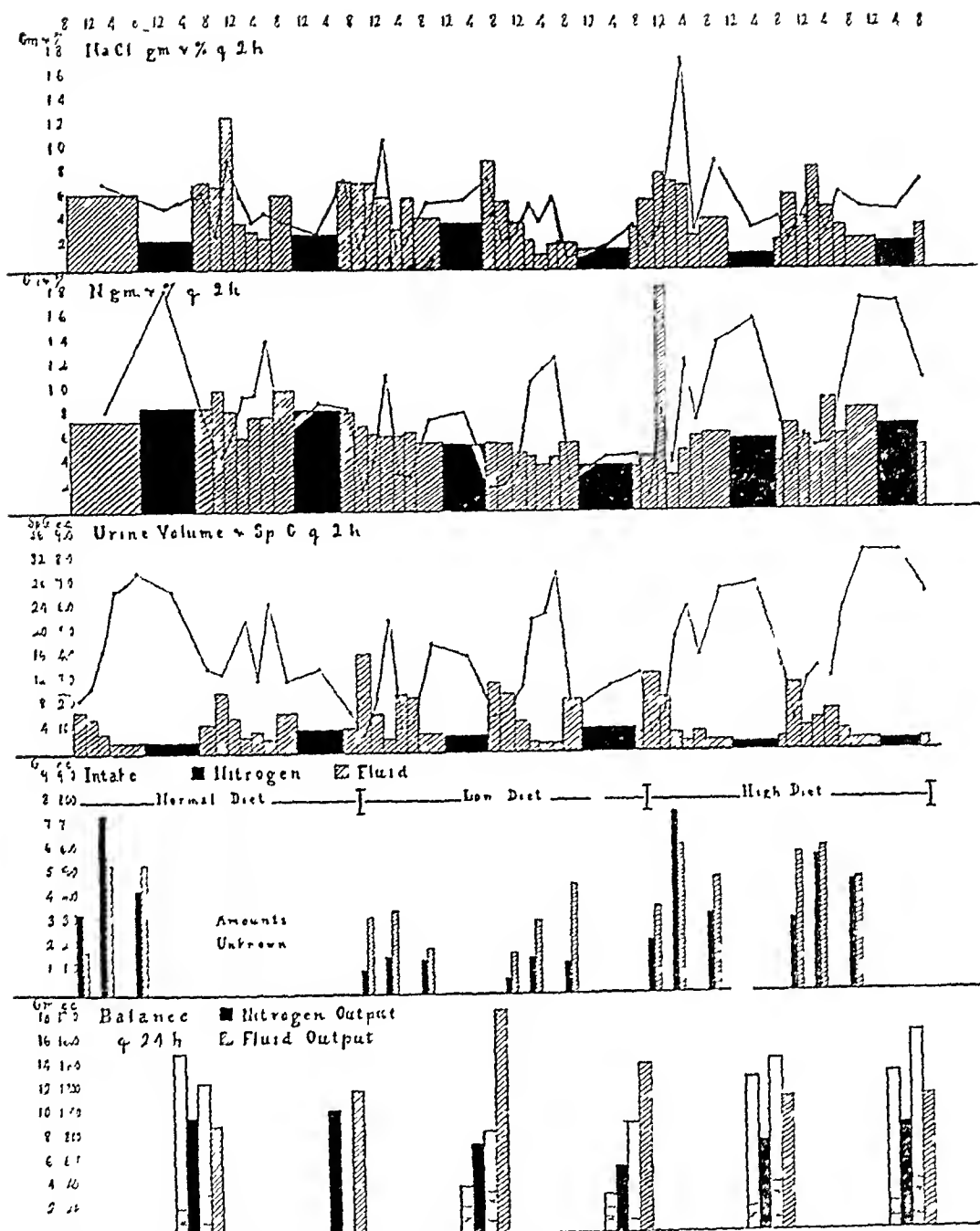


Chart 1—Results of frequent collections of urine in the day time and a single specimen of urine at night in a normal individual for a period of six days. It shows how the variations of volume of urine, specific gravity and concentration of NaCl and N are somewhat similar whether the diet is normal, low or high.

Explanation of the Chart The height of the columns in the spaces for NaCl, N and urine volume indicate the two-hourly rate of excretion (they are not absolute values as in the remaining charts), the width of each column represents the period of time covered by the individual specimen, the night urines are indicated in the solid black, the day specimens in oblique hatching. The dots joined by continuous lines crossing the upper three tiers from left to right indicate the percentage concentrations of NaCl and N and the specific gravity, respectively. In the second tier the columns represent absolute values for N and fluid taken at each meal. The dividing line between the solid black (N) and cross hatched (fluid) column indicates the time at which the meal was taken. The columns in the first tier record the fluid and N balance for the preceding twenty-four hours.

results, because of their great interest and importance for the more thorough understanding of the normal mode of action of the kidney, are given in full in Table 6

TABLE 6—RESULTS IN NORMAL PERSONS WHILE FASTING

Observation 1 First Day of Starvation

Water Intake		Urine						
Time	O O	Time	O O	Sp Gr *	NaCl		N	
					%	Gm	%	Gm
8	200	8 10	245	11	0 64	1 57	0 49	1 20
10	200	10-12	345	08	0 52	1 79	0 81	1 07
12	200	12 2	92	15	0 82	0 75	0 89	0 82
2	200	2 4	92	18	0 52	0 48	0 92	0 85
4	200	4 6	390	07	0 16	0 62	0 26	1 01
6	200	6 8	132	17	0 50	0 66	0 89	1 17
Total, day	1,200		1,296			5 87		6 12
Night	0	8- 8	295	27	0 74	2 18	1 69	4 99
Total, 24 hours	1,200		1,591			8 05		11 11

Observation 2 First Day of Starvation

Water Intake		Urine						
Time	O O	Time	O O	Sp Gr *	NaCl		N	
					%	Gm	%	Gm
8	250	8-10	100	17	1 02	1 02	0 76	0 76
10	250	10-12	45	22	0 78	0 35	1 13	0 51
12	250	12 2	56	22	0 96	0 53	1 16	0 65
2	250	2 4	268	05	0 18	0 48	0 30	0 80
4	250	4- 6	202	08	0 16	0 32	0 40	0 81
6	250	6 8	174	08	0 16	0 28	0 38	0 66
Total, day	1,500		845			2 98		4 19
Night 8	250	8- 8	900	10	0 16	1 44	0 49	4 41
Total, 24 hours	1,750		1,745			4 42		8 60

Observation 3 First Day of Starvation

Water Intake		Urine						
Time	O O	Time	O O	Sp Gr *	NaCl		N	
					%	Gm	%	Gm
8	250	8-10	40	27	0 66	0 26	1 37	0 55
10	250	10 12	325	04	0 38	1 24	0 25	0 81
12	250	12 2	450	04	0 34	1 53	0 16	0 72
2	250	2- 4	205	06	0 32	0 66	0 30	0 62
4	250	4 6	178	05	0 24	0 43	0 29	0 52
6	250	6 8	204	05	0 22	0 45	0 22	0 45
Total, day	1,500		1,402			4 57		3 67
Night	0		257	20	0 42	1 08	0 94	2 42
Total, 24 hours	1,500		1,659			5 65		6 09

TABLE 6—RESULTS IN NORMAL PERSONS WHILE FASTING—*Continued*

Observation 4 Second Day of Starvation

Water Intake		Urine						
Time	O O	Time	O O	Sp Gr *	NaCl		N	
					%	Gm	%	Gm
8	250	8-10	70	21	0.24	0.17	0.95	0.67
10	250	10-12	110	18	0.26	0.29	0.78	0.86
12	250	12-2	158	14	0.22	0.35	0.58	0.92
2	250	2-4	440	05	0.10	0.44	0.22	0.97
4	250	4-6	295	06	0.14	0.41	0.27	0.80
6	250	6-8	234	08	0.22	0.51	0.32	0.75
Total, day	1,500		1,307			2.17		4.97
Night	0	8-8	770	15	0.20	1.54	0.56	4.31
Total, 24 hours	1,500		2,077			3.71		9.28

Observation 5 First Day of Starvation

Water Intake		Urine						
Time	O O	Time	O O	Sp Gr *	NaCl		N	
					%	Gm	%	Gm
8	150	8-10	50	20	0.95	0.48	1.01	0.51
10	150	10-12	104	17	1.14	1.19	0.78	0.81
12	150	12-2	77	17	1.15	0.89	0.85	0.65
2	150	2-4	115	13	0.72	0.83	0.73	0.84
4	150	4-6	65	20	0.84	0.55	1.03	0.67
6	150	6-8	96	15	0.52	0.50	0.77	0.74
Total, day	900		507			4.44		4.22
Night	0	8-8	308		0.54	1.66	1.58	4.87
Total, 24 hours	900		815			6.10		9.09

Observation 6 First Day of Starvation

Water Intake		Urine						
Time	O O	Time	O O	Sp Gr *	NaCl		N	
					%	Gm	%	Gm
8	350	8-10	95	25	1.78	1.69	0.73	1.69
10	350	10-12	405	06	0.26	1.05	0.15	0.61
12	175	12-2	300	06	0.36	1.98	0.22	0.66
2	175	2-4	340	06	0.22	0.75	0.15	0.52
4	175	4-6	135	10	0.60	0.81	0.36	0.49
6	175	6-8	34	16	0.94	0.32	0.60	0.20
Total, day	1,400		1,309			6.60		4.17
Night	0	8-8	150	23	0.82	1.23	0.93	1.40
Total, 24 hours	1,400		1,459			7.83		5.57

TABLE 6—RESULTS IN NORMAL PERSONS WHILE FASTING—*Continued*

Observation 7 Second Day of Starvation

Water Intake		Urine		
Time	C C	Time	C C	Sp Gr *
8	175	8-10	34	27
10	175	10-12	102	12
12	350	12-2	122	10
2	350	2-4	385	05
4	175	4-6	375	05
6	0	6-8	202	07
Total, day	1,225		1,220	
Night	0	8-8	460	22
Total, 24 hours	1,225		1,680	

Observation 8 Second Day of Starvation

Water Intake		Urine		
Time	C C	Time	C C	Sp Gr *
Not Noted		8-10	77	24
		10-12	45	25
		12-2	61	25
		2-4	44	26
		4-6	60	25
		6-8	63	26
Total, day	?		353	
Night	?	8-8	475	17
Total 24 hours	?		828	

* Last two figures only

It is evident that even in starvation there is a maximum concentration of 1 020 or over. This would not have been the case had water been forced continuously, as has been done by a number of observers. Under such conditions there is a continuous flow of urine of low specific gravity. In the present studies only such amounts of water as the person was supposed to desire were taken at regular intervals, thus providing a constant stimulus to diuresis. Under such circumstances there appear to be two types of response, one seen in Observation 8 (Table 6), the other in the remaining experiments. In Observation 8 there was no record of the water intake, presumably, however, it was low, as the specific gravity remained high and fairly constant throughout the day, Observation 5, with a comparatively low water intake (150 cc every two hours) approximates this result. In the other observations, when the water intake was higher, there was at least one specimen in the twenty-four hours that reached 1 021 or higher. This is in large part due to the fact that in spite of the constant water intake,

there was at intervals a large urine output, exceeding the intake by a considerable margin, followed by a period of comparative oliguria. It seemed as though, if the resistance which the diuretic stimulus encountered were once overcome, the kidney continued to act and drain the body of as much fluid as was available, acting much on the principle of a syphon. Thus, there would be either one (Observations 2, 3, 4, 6 and 7, Table 6, and Observation 4, Chart 2) or two periods of diuresis (Observation 1, Table 6, and Chart 2) during the day.

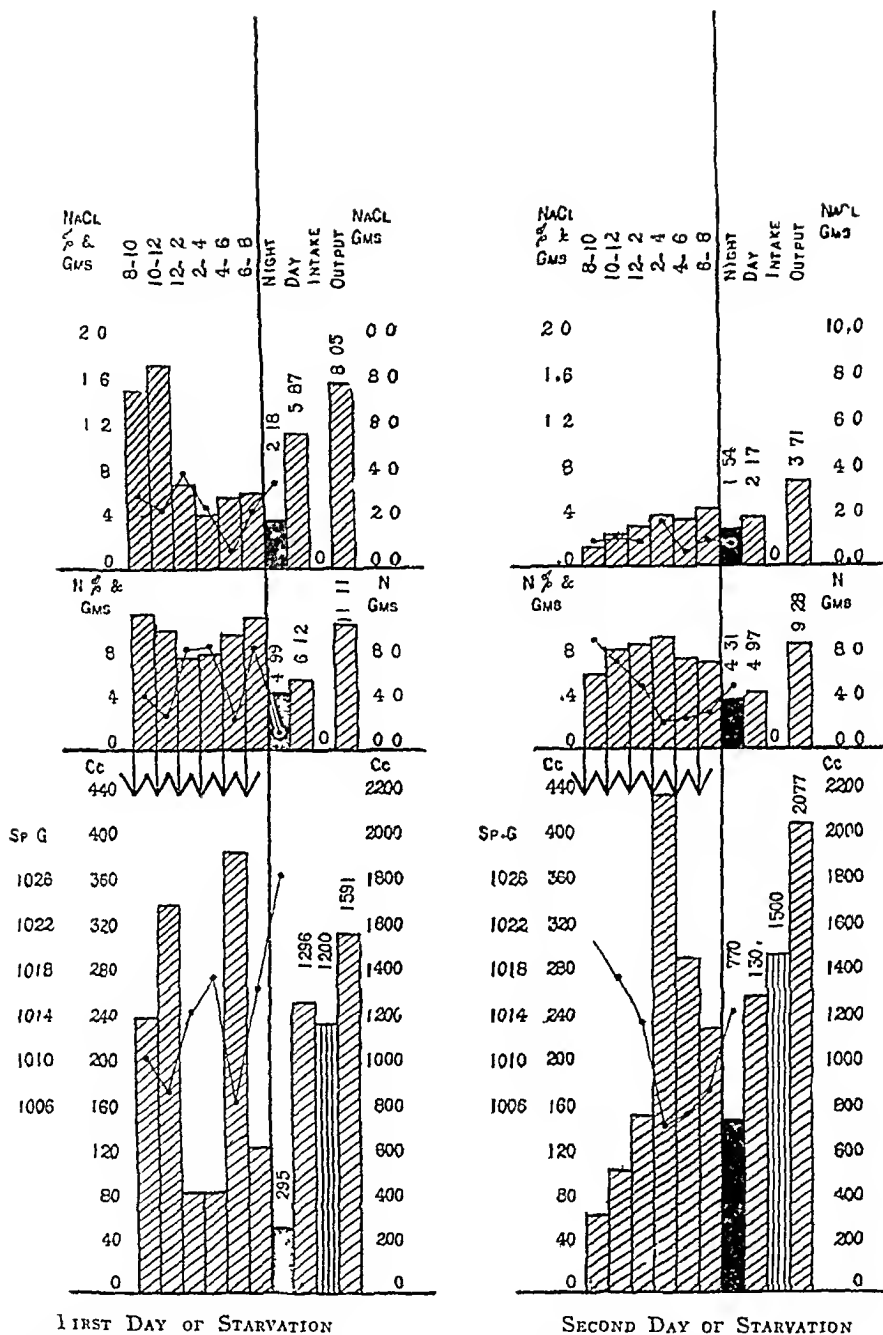
That the specific gravity varies in inverse proportion to the quantity of fluid excreted is readily appreciated. It is this factor of variability in the water output, in spite of a constant fluid intake, that evidently is, in part at least, responsible for the production of a specific gravity of 1.020 or over during some period of the day or night in normal persons. The quantity of nitrogen excreted remains fairly constant from period to period, being at times slightly higher when diuresis occurs. The sodium chlorid has a tendency to be much higher in the morning hours than in the afternoon on the first day of starvation. Here again during the period of high urine output the salt excretion is frequently, though not always, raised. These facts are brought out clearly in Chart 2. The one observation (Observation 4, Table 6 and Chart 2) covering the second day of starvation indicates that the sodium chlorid output becomes constant from hour to hour at that time.

Explanation of the Charts—Except Charts 1 and 4, each chart is divided by two horizontal lines into three tiers. The lowest of these gives the figures for water and specific gravity, the middle for nitrogen and the upper for sodium chlorid. Each is further divided by a central vertical line into right and left halves. The left half, with its scale at the extreme left, contains six columns for the two-hourly specimens collected between 8 a. m. and 8 p. m. Each column represents absolute values. The right half is read by the scale at the extreme right. The columns of this right half are two pairs, the central pair represents the total night and the total day twelve-hour figures for volume, nitrogen and sodium chlorid, night in solid black and day in oblique hatching at its right. The pair at the extreme right represent intake and output for the whole twenty-four hours, intake at the left in vertical, output at the right in cross or oblique hatching. The dots joined by continuous lines crossing each tier from left to right indicate the specific gravity and the percentage concentrations of nitrogen and sodium chlorid, respectively, and are read from the scale at the left.

It seems justifiable to conclude, therefore, that a normal individual will void at least one specimen a day, when the urine is collected according to the method under discussion, of a specific gravity of 1.018 or more on any diet, and of 1.020 or higher on the low or normal diets.

THE VARIATION OF SPECIFIC GRAVITY IN NORMAL TESTS

From Tables 2, 3, 4 and 5 it is evident that in normal individuals there is usually a variation of specific gravity of 9 points or more while on the high and low diets, but that the variation may be much less on



↓ Indicates the time at which 200 cc of fluid were taken (corresponds to Observation 1, Table 6)

↓ Indicates the time at which 250 cc of fluid were taken (corresponds to Observation 4, Table 6)

Chart 2—Results of two-hourly collections of urine in the day time and a single specimen at night in normal individuals, while taking no food or fluid except water. Note the marked variations in the volume and specific gravity, and the concentrations of N and NaCl in the urine, in spite of the constant fluid intake.

the normal diet. It would seem that this is largely a matter of the amount of fluid taken during the day. This is comparatively high with the low protein diet, in which the vegetables, cereals and fruits contain much moisture, in the high diet it is forced to some extent, although even here, during hot weather, especially when there is much water lost through the skin, as Lyle and Shalitz have shown, and as is noted in the present observations, the amount of water consumed is inadequate to result in much variation in the amounts of urine eliminated, and the result may be a distinct fixation of specific gravity, though this occurs but rarely, and always at a high level, with the normal diet, however, the results are distinctly different, and there is a marked tendency to a fixation of the specific gravity. Evidently, under ordinary circumstances, the normal individual is in the habit of taking less fluid than when consuming the food which we have been accustomed to use in the low and high diet tests. It has been previously mentioned that a kidney apparently affected by a constant diuretic stimulus of frequently repeated drinks of water of moderate size will exhibit periods of polyuria and oliguria (Table 6 and Chart 2), and that this variation in the specific gravity in the specimens of urine obtained from hour to hour appears to be one of the characteristics of a normally functioning kidney when receiving an adequate supply of water, regardless of the diet. It may be concluded, therefore, that under the conditions of the test a normal urine is one which exhibits a variation of specific gravity of 9 degrees or more. A smaller variation does not necessarily indicate that the kidney is abnormal, provided the specific gravity is high (1.020 or over), but may point to a deficient available supply of water from which to form urine. It may prove itself of value in appropriate cases to use this method to determine whether or not an individual is drinking enough water to meet his bodily demands.

THE VOLUME, SPECIFIC GRAVITY AND CONCENTRATION OF NITROGEN OF THE NIGHT URINE IN NORMAL TESTS

The main error of the former normal standard lay in the fact that the volume of the night urine was thought to be 400 c c or less. Lyle and Shalitz have already pointed out that this is incorrect. The present studies (Tables 2, 3, 4 and 5) indicate that the night urine, when the collection of this specimen is begun three hours after supper, and no further food or fluid is taken until the next breakfast, may be as high as 750 c c, regardless of whether the diet be high, low or normal. If this be true, it necessarily follows that the night urines exhibit lower specific gravities and lower concentrations of nitrogen than was originally thought possible. In judging the night specimen, therefore, only urines exceeding 750 c c may be looked on as exhibiting nocturnal

polyuria, the specific gravity figures can only be regarded as of any value, in so far as they may, in some cases, be the maximal concentration of the test, the concentration of nitrogen may be interpreted as normal if it is over 1 per cent, but not necessarily as an indication of diminished renal function, if it is lower

THE REVISED NORMAL STANDARD

The normal standard, as discussed in the foregoing for the various diets, is summarized in Table 7. It would seem from these tabulations (Tables 2, 3, 4 and 5), with some minor differences as indicated in Table 7, and the very obvious conclusion that a high concentration of salt and nitrogen is less frequent on the low than on the other diets,

TABLE 7—NORMAL STANDARD FOR TEST MEAL FOR RENAL FUNCTION

	Diet		
	High	Low	Normal
Maximum specific gravity	18+	20+	20+
Degrees variation of specific gravity, usually	9+	9+	No value
Specific gravity of night urine	Of no significance		
Volume cc of night urine	750 cc or less		
Na and NaCl per cent in night urine } or highest per cent in any specimen }	{ Normal if 1 per cent or higher, not necessarily abnormal if less		

that the diets may be used interchangeably for the test. When the significance of the factors already discussed is more thoroughly understood, various simpler methods will perhaps be devised to test out one point or the other that may seem especially important. The summary given in Table 7 would indicate that the height of the maximum specific gravity and the volume of the night urine are the most constant features of the normal test, regardless of the diet. The other characteristics are possibly robbed of some, but not all, of their significance, because they fluctuate within such wide limits.

TEST MEALS FOR RENAL FUNCTION ON HIGH AND LOW DIETS IN
ABNORMAL INDIVIDUALS

The comparative value of test meals for renal function on high and low diets was observed in 114 patients whose diagnoses are detailed in Table 8. In the study of these cases only the high and low diets were employed. It was thought that these would probably yield results with the greatest possible contrast. "Normal" diets are usually impracticable in the class of patients under consideration. The only possible disturbing element, if other diets than these would be employed in carrying out the test, would appear to be the greater tendency to a

fixation of the specific gravity (Table 5) Due allowance can be readily made for this variation The tests under consideration are so numerous that only a summary of them can be presented The findings previously reported² for diseases of the urinary tract have been thoroughly substantiated, and only such facts as appear to be new will be completely discussed

TABLE 8—CASES IN WHICH A COMPARISON OF TEST MEALS ON HIGH AND LOW DIETS WAS MADE

Diagnosis	Number of Cases	
Chronic nephritis	58	}
Essential hypertension	21	
Acute nephritis	13	
No renal disturbance	6	
Pyelitis and cystitis	4	
Cardiac disease	4	
Marked anemia	3	
Hyperthyroidism	3	
Spinal cord injury and paralysis of bladder	1	
Polycystic kidneys	1	
	114	

NOCTURNAL POLYURIA

There were twenty-one patients of the 114 studied in whom there was a nocturnal polyuria (that is, more than 750 c c of urine at night) on only one of the tests It is very significant that the increase of night urine occurred almost exclusively on the high diet (Table 9) In only two of the twenty-one cases in question was it found with the low diet test, in one of these the patient was evidently eliminating edema at the time he was exhibiting a nocturnal polyuria and may therefore be considered as being under diuretic influences, which nullified those of the diet, there was no evident explanation for the occurrence of the increased volume of night urine on the low diet in the second case, the one diagnosed as hypertension

It is self evident that there should be a greater elimination of salt and nitrogen on the days of the high diet than on the low This increased excretion is likewise present in the corresponding night urine (Table 9) This simple fact throws much light on the question of nocturnal polyuria, which has thus far been largely accepted as a symptom for which there was no definite explanation It may be noted that in both instances in which the nocturnal polyuria occurred during the low diet period there was an increased elimination of salt and, in one case, an increased excretion of nitrogen, as compared to the high diet period It would then appear that the quantity of solids which the kidney was eliminating might be considered the determining factor controlling the amount of night urine In the first place, it may be concluded that nocturnal polyuria is a compensatory phenomenon to bring about the elimination of solids which a defective kidney

cannot excrete except at lower concentrations than normal, in the second place, it appears that nocturnal polyuria is a signal that the kidney function is being overtaxed and that, in some instances at least, a suitable diet may do away with this unnecessary strain

TABLE 9—COMPARISON OF NIGHT URINES IN THOSE CASES IN WHICH THERE WAS NOCTURNAL POLYURIA (MORE THAN 750 CC) ON ONLY ONE OF THE TEST DIETS

Diagnosis	Phenol sulphone phthalein, Per Cent	Night Urine					
		Low Diet			High Diet		
		Volume, C C	NaCl Gm	N Gm	Volume, C C	NaCl Gm	N Gm
Chronic nephritis	0	720	2 02	3 67	840	2 86	4 12
Chronic nephritis	10	475	1 62	2 09	1055	4 01	3 69
Chronic nephritis	16	590	2 12	2 42	925	3 52	2 87
Chronic nephritis	20	535	2 68	2 14	1147	6 07	6 07
Chronic nephritis	31	740	4 22	4 00	790	4 66	4 19
Chronic nephritis	32	400	1 28	3 20	780	3 20	5 30
Chronic nephritis	37	610	4 03	2 68	1300	8 32	4 29
Chronic nephritis	39	470	2 44	1 44	820	5 58	4 02
Chronic nephritis	39	1000	5 40	3 50	335	2 61	3 47
Chronic nephritis	45	595	1 79	2 02	1910	4 39	5 73
Chronic nephritis	46	525	1 10	4 52	1170	2 46	4 68
Essential hypertension	63	415	4 07	4 57	900	9 18	7 11
Essential hypertension	66	1040	4 68	2 70	550	3 58	4 02
Essential hypertension	57	565	4 80	2 88	767	5 52	4 60
Essential hypertension	59	725	4 35	2 32	1240	9 18	5 08
Acute nephritis	24	440	1 36	2 68	860	3 27	5 07
Acute nephritis	35	740	3 26	2 59	1160	4 64	4 18
Acute nephritis	61	660	1 65	3 17	795	1 91	3 98
Pyelitis and cystitis	65	415	1 83	2 78	780	3 98	3 59
Anemia		520	2 81	1 82	1250	2 75	6 34
Chronic arthritis	75	507	2 26	2 86	1004	5 75	4 66

A detailed example of these phenomena is given in Table 10 and Chart 3. This was a case of chronic nephritis of moderate severity. The tests on the low diet and the high diets show absolute agreement except for the presence of nocturnal polyuria on the high diet and none on the low. There is a distinct fixation of specific gravity at a rather low level— ± 1.014 , the concentrations for salt and nitrogen do not rise very high and are fairly constant, and the output of fluid during the day is approximately the same in both instances, in the night urine, however, the high diet test shows a volume of 780 cc, containing 3.2 gm of sodium chlorid and 5.3 gm of nitrogen, as con-

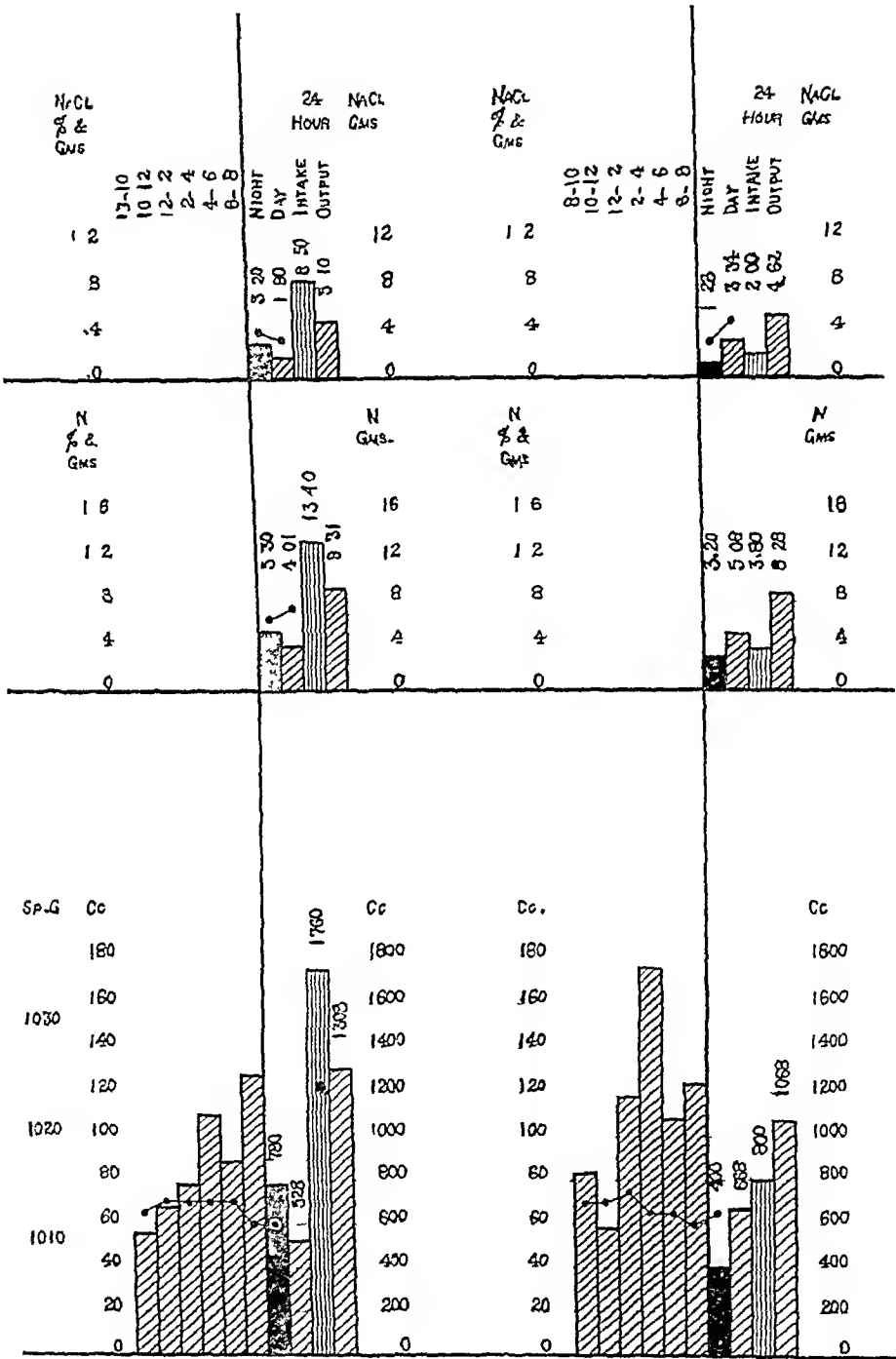
trasted with 400 c c , sodium chlorid, 1 28 gm , and nitrogen, 3 2 gm , on the low diet Since the concentrations of sodium chlorid and nitrogen in the urine did not vary appreciably, it would appear that the nocturnal polyuria here is a distinct compensatory manifestation to eliminate the solids which would otherwise have been retained

TABLE 10—RESULTS WITH HIGH AND LOW DIETS IN A CASE OF CHRONIC NEPHRITIS OF MODERATE SEVERITY THE TESTS ARE IN ABSOLUTE AGREEMENT EXCEPT THAT NOCTURNAL POLYURIA IS PRESENT ON THE HIGH DIET AND NOT ON THE LOW DIET THIS IS A VERY COMMON DISCREPANCY (THE FIGURES CORRESPOND WITH CHART 3)

Time of Day	O C	Specific Gravity	Sodium Chlorid		Nitrogen		Albumin, Per Cent
			Per Cent	Grams	Per Cent	Grams	
8-10	56	1 013					
10 12	68	1 014					
12 2	78	1 014					
2 4	110	1 014					
4- 6	88	1 014					
6- 8	128	1 012					
Total, day	528		0 36	1 90	0 76	4 01	Faint trace
Night, 8 8	720	1 012	0 41	3 20	0 68	5 30	Faint trace
Total, 24 hrs	1,308			5 10		9 31	
Intake	1,760			8 50		12 40	
Balance	+452			+3 40		+4 09	

Time of Day	C C	Specific Gravity	Sodium Chlorid		Nitrogen		Albumin, Per Cent
			Per Cent	Grams	Per Cent	Grams	
8 10	84	1 014					
10 12	58	1 014					
12 2	118	1 015					
2 4	176	1 013					
4 6	108	1 013					
6 8	124	1 012					
Total, day	668		0 50	3 34	0 76	5 08	Faint trace
Night, 8-8	400	1 013	0 32	1 28	0 80	3 20	Faint trace
Total, 24 hrs	1,068			4 62		8 28	
Intake	800			2 00		3 80	
Balance	-268			-2 62		-4 48	

It has been generally believed that polyuria, in chronic nephritis and other conditions, is a favorable symptom, provided that it results in an adequate excretion of solids in the urine, and dietetic measures have as a rule not been directed against it In diabetes insipidus we



High Diet Test Low Diet Test

Chart 3—Results with high and low diets in a case of chronic nephritis of moderate severity. The tests are in absolute agreement except that nocturnal polyuria is present on the high diet and not on the low diet. This is a very common discrepancy.

have an example of the most extreme polyuria which apparently does not damage the kidney. Cases of chronic nephritis, however, present a different problem, in them it may very well be that overstrain of the function of water excretion may result in further damage to the kidneys. While the present observations do not furnish conclusive evidence on this point, it is interesting to note that many of these patients welcomed the low protein diet because it relieved their thirst to such a great degree. To them the polyuria appeared to be a secondary consideration. Furthermore, in one instance, at least, an accidental observation showed that water given in large amounts may result in a diminished urinary output instead of an increase (Chart 4). Similar phenomena have been recorded as the result of diuretic drugs and sodium chlorid. That a diuretic as bland as water should "fatigue" the kidney is probably somewhat surprising. In another instance of severe nephritis, the same phenomenon was seen as the result of a glucose infusion. It may be that a polyuria persisting for a longer period may cause a gradual impairment of renal function, just as the sudden huge increase of water intake in the instances cited in the foregoing brought about an immediate diminution in the volume of urine. These facts must be looked on as suggestive only, unless they are borne out by further evidence. There were nine cases of chronic nephritis in the present series exhibiting nocturnal polyuria on both diets, their phenolsulphonephthalein excretion ranged from 35 to 5. The eleven cases in which the abnormally high night urine was present on only one diet (almost invariably on the high diet, Table 9) showed a phenolsulphonephthalein varying from 46 to 0. The remaining cases of chronic nephritis, thirty-eight in number, in which there was a night urine, normal in amount, on both the high and the low diets, revealed phenolsulphonephthalein excretions varying from 0 to 58 per cent in two hours. Of the twenty-one cases classified as hypertension, in which the phenolsulphonephthalein was approximately normal, there was nocturnal polyuria on the low diet in one case, on the high diet in three cases, and no nocturnal polyuria on either diet in seventeen cases. From these facts it may be concluded that nocturnal polyuria may be absent even when there is a very marked renal insufficiency, but that when it is present it indicates a distinct impairment of function, especially if the night urine is increased while the patient is on a low diet.

As has been stated before, the interpretation and therapy of any one of these abnormalities depend largely on the cause. An entirely different significance is to be attributed to nocturnal polyuria in chronic and acute nephritis, pyelitis, cystitis, severe anemia, diabetes insipidus, etc. In general, nocturnal polyuria was found to exist in the same type of cases as in the observations previously recorded.

THE MAXIMAL SPECIFIC GRAVITY

This is probably one of the most important features in measuring renal function by the method under consideration. It has been previously noted how, as the activity of the kidney becomes impaired, there is a tendency for the specific gravity of the urine to assume a lower level until in the final stages it usually cannot be raised above 1.010. In the present studies it has been shown that in the normal individual the test meal for renal function elicits a maximal specific gravity of 1.018 or over on the high diet and of 1.020 or more on the low (Table 5). In comparing the results of the high and low diet, as far as the maximal specific gravities are concerned, in abnormal individuals, there is a fairly close agreement (Table 11).

As is shown by the figures in heavy type in the comparative statistics given in Table 11, there is more than a very slight disagreement in the conclusion to be drawn from the maximal specific gravity on the high and low diets in only sixteen out of the 114 tests, and in most of these the difference is not very great. There are, however, a few in which there is a marked divergence between the two. In a number of these it is the very rapid change which renal function undergoes in patients in whom there is an edema, either because of passive congestion brought on by myocardial insufficiency, or as an accompaniment of either chronic or acute nephritis. In all of these conditions, which are so closely related to the question of renal function, both in chronic and acute nephritis, there is nearly always a specific gravity of about 1.020, which is usually fairly fixed. The change from an oliguric state to one in which there is a polyuria and an elimination of the retained fluid, is often, though not always, a very rapid one. This very sudden increase in the quantity of urine elimination is accompanied by a corresponding depression in the specific gravity. This, instead of being constantly high, now becomes fixed at a low level. In two cases, a record of the urinary excretion by the test meal method was fortunately obtained on the day when the polyuria set in. In the first patient there had been a very marked and persistent edema for more than four months, he was suffering with an acute nephritis which was becoming chronic. Table 12 and Chart 5 show how rapidly in his case the transformation occurred from one specimen to the next, it may be considered to be a matter of minutes only. Another patient, a case of acute nephritis, exhibited this same sudden remarkable change (Table 13). It is probable that most of the very marked differences occurring in maximal specific gravities of the high and low test meals are accounted for in this way. The findings in regard to the above phenomenon have been so constant that from a single specimen it was often

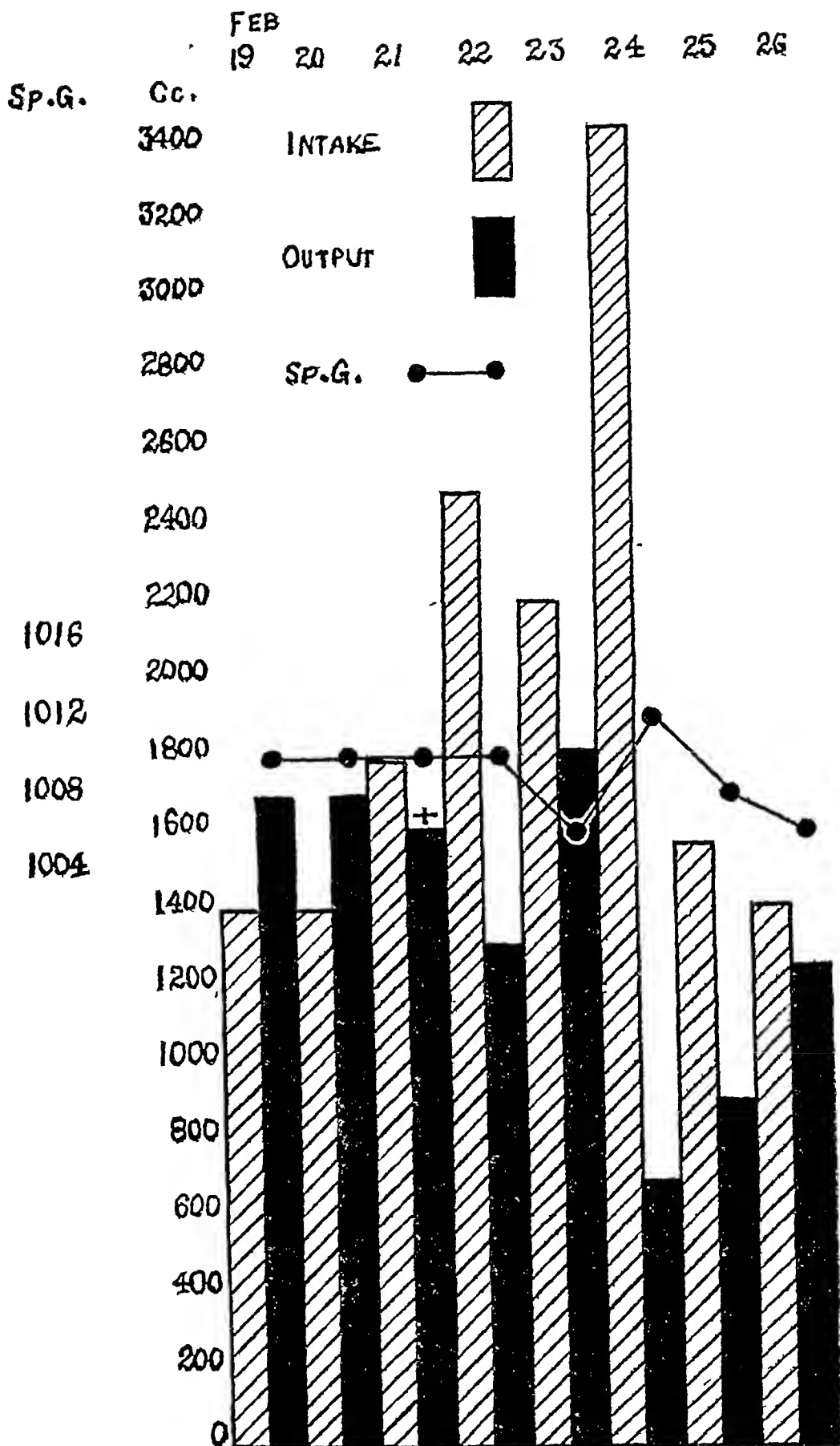


Chart 4—The result of forcing fluids in a case of marked chronic nephritis (The low, fixed specific gravity is seen in the chart, the phenolsulphonephthalein excretion was 5 per cent in two hours) The large fluid intake did not bring about an increased output of urine, but evidently had the opposite effect, indicating that what we consider to be the blandest of all diuretics, water, may, if given in excess, cause further impairment of renal function in severe nephritis

TABLE 11—COMPARISON OF THE MAXIMAL SPECIFIC GRAVITIES OBTAINED ON THE HIGH AND LOW DIETS IN ABNORMAL PERSONS*

Diagnosis	Number of Cases in which Both Tests Are Normal†	Cases in which the Maximal Specific Gravity is Below Normal in One Test Only			Cases in which the Maximal Specific Gravity is Below Normal in Both Tests		
		Maximal Specific Gravity‡		Phenol sulphone-phthalein Per Cent in Two Hours	Maximal Specific Gravity§		Phenol sulphone-phthalein Per Cent in Two Hours
		Low Diet	High Diet		Low Diet	High Diet	
Chronic nephritis	16	(16) (18) 29 22 (19) 22 (18) (19) (19) (17)	21 19 (17) (14) 22 (17) 20 19 18 18	65 55 53 47 44 41 41 37 30 29	13 15 18 14 15 17 17 16 11 09 19 15 14 14 12 15 14 19 10 10 10 10 10 10 10 10 13	16 12 15 09 16 15 15 11 11 12 15 14 15 12 13 12 12 13 14 11 17 17 11 11 09 12 08 08 10 11 14	60 58 46 46 45 45 44 40 36 35 34 32 31 30 30 29 21 20 20 20 16 16 12 10 10 8 5 5 5 0 0
Acute nephritis	0	(17) (14) (15)	19 21 18	72 50 34	09 14 13 16 16 13 15 15 17 13	12 14 12 17 15 15 15 15 15 14	61 60 54 54 53 50 40 35 35 24
Essential hypertension	11	20 (15) (10) (19) 21 (19) (14)	(17) 18 20 20 (14) 20 18	69 68 67 65 57 51 46	14 19 15	17 15 15	81 59 49
Polycystic kidneys	0				10	10	0
Cystitis and pyelitis	1	(17)	19	70	10 09	11 11	60 57
Cardiac disease	2	(19) (19)	26 25	60 31			
Anemia	1	26	(15)	55	12	14	73
Hyperthyroidism	2				17	17	
Spinal cord lesion and bladder paralysis	0				14	12	0
No renal lesion	3	25 29	(17) (17)	75 72	19	17	63

* Only the last two figures of the specific gravity are charted

† 1018+, on high diet, 1020+, on low diet

‡ The figure in parenthesis is the abnormal one. Instances in which the abnormal figure is more than 2 points below normal are printed in heavy type

§ Instances in which the variation between the maximal figures of the two diets is 4 or over are printed in heavy type

TABLE 12—RESULTS IN A CASE OF ACUTE NEPHRITIS WITH EDEMA THE EDEMA HAD PERSISTED FOR ABOUT FOUR MONTHS ON THE DAY OF HIGH DIET THE VERY SUDDEN CHANGE TO POLYURIA WITH A MUCH LOWERED SPECIFIC GRAVITY MAY BE NOTED ON THE LOW DIET THE MARKED SUCCESS OF THE KIDNEY IN ELIMINATING EDEMA IS EVIDENT THESE CHANGES IN EDEMATOUS CASES FREQUENTLY ARE RESPONSIBLE FOR VERY VARYING RESULTS (THE FIGURES CORRESPOND WITH CHART 5)

Time of Day	C C	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	Grams	Per Cent	Grams
8-10	102	1 017	0 89	0 91	0 50	0 51
10-12	90	1 020	0 83	0 75	0 63	0 61
12- 2	98	1 020	0 63	0 62	0 78	0 76
2- 4	118	1 021	0 47	0 55	0 81	0 96
4- 6	88	1 020	0 42	0 37	0 83	0 77
6- 8	330	1 006	0 17	0 66	0 26	1 01
Total, day	838			3.86		4 62
Night, 8-8	1,280	1 010	0 49	6 26	0 23	4.86
Total, 24 hrs	2,166			10 12		9 48
Intake	1,760			8 50		13 40
Balance	-406			-1 62		-3 92

Time of Day	C C	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	Grams	Per Cent	Grams
8-10	355	1 010	0 66	2.34	0 20	0 71
10-12	195	1 014	0 90	1 76	0 34	0 66
12- 2	290	1 011	0 64	1.86	0 28	0 81
2- 4	225	1 014	0 77	1 73	0 35	0 79
4- 6	186	1 014	0 89	1 60	0 37	0 67
6- 8	275	1 010	0 53	1 60	0 31	0 85
Total, day	1,520			10.89		4 48
Night, 8-8	1,660	1 010	0 60	9 96	0 21	3 49
Total, 24 hrs	3,180			20.85		7 97
Intake	680			8 50		3 89
Balance	-2,500			-12 35		-4 03

possible to determine whether the edema was retained (specific gravity ± 1.020) or eliminated (specific gravity $= 1.010$)

At times this transition from a marked oliguria to a pronounced polyuria is not so abrupt. The case of which tests are given in Table 14 and Chart 6 illustrates this. This was a patient afflicted with a marked chronic nephritis, accompanied by a moderate degree of edema. There is no very marked difference between the two tests except that on the day of high diet the specific gravity was fixed at a lower level ($= 1.011$) than on the low ($= 1.014$).

TABLE 13—RESULT OF TEST MEAL ON HIGH DIET IN A CASE OF ACUTE NEPHRITIS. THE SHARP CHANGE FROM OLIGURIA WITH A HIGH SPECIFIC GRAVITY TO POLYURIA AND A LOW SPECIFIC GRAVITY IS STRIKING. THIS IS PRESUMABLY THE EXACT TIME AT WHICH THE KIDNEYS BEGAN TO ELIMINATE THE EDEMA.

Time of Day	C C	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	Grams	Per Cent	Grams
8-10	40	1.021				
10-12	63	1.021				
12-2	25	1.020				
2-4	57	1.018				
4-6	83	1.017				
6-8	223	1.009				
Total, day	596	..	0.57	2.53	0.65	2.24
Night, 8-8	1,223	1.010	0.50	6.14	0.33	4.65
Total, 24 hrs	1,724		..	9.02		7.29
Intake	1,760	2.09		13.40
Balance	+26		.	-6.02		-6.61

This would seem to indicate that fluid was being more readily eliminated in the first period. There is not much difference in the fluid balances of the two days. (It has already been noted how on the low diet because of the fluid contained in the vegetables, fruits and the boiled cereals and puddings, there is an apparently negative fluid balance in normal individuals. The small water loss on the low diet day may, therefore, be considered to be within normal limits.) It is probable, however, that the retention of fluid was responsible for the test in which the specific gravity was 1.014 and that the elimination of the edema resulted in the urinary specimens with a specific gravity of 1.011.

It must be borne in mind in this connection that cases of very severe nephritis may not show an elevation of the specific gravity in spite of a failing heart and congestion of the kidneys, or because of the accumulation of edema associated with renal disease. These

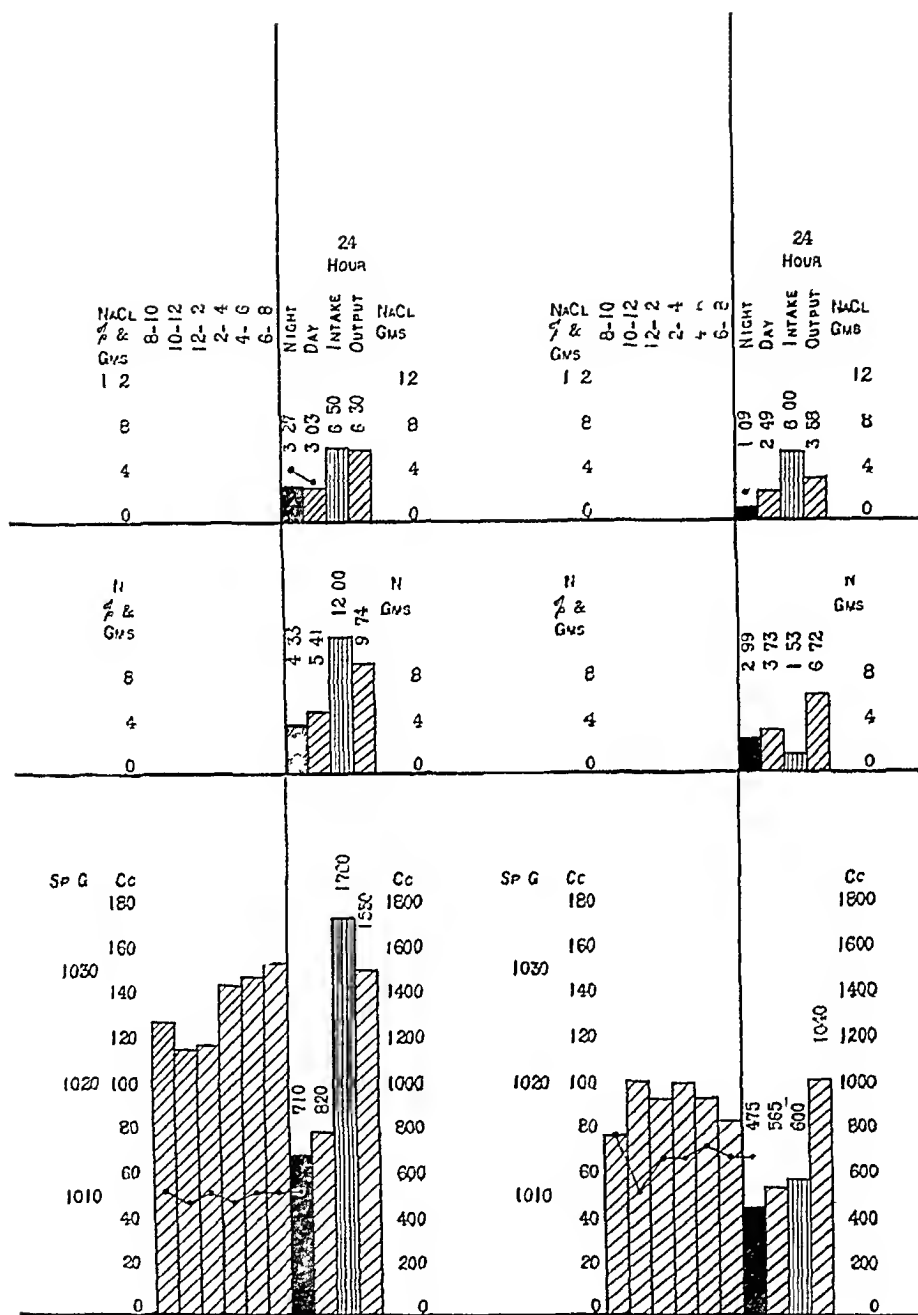


Chart 6—Results with high and low diets in an advanced case of chronic nephritis with edema. It is probable that the varying reaction of the kidney to the retained fluid is responsible for the difference in the two tests. Here the changes are not as abrupt as in Tables 12 and 13. The maximal specific gravity on the low diet is moderately lower than normal, that on the high diet is markedly so.

are among the most advanced types of diminished renal function met with, and in them the maximal specific gravity is always at a level of about 1 010. This accounts for the very marked agreement of the

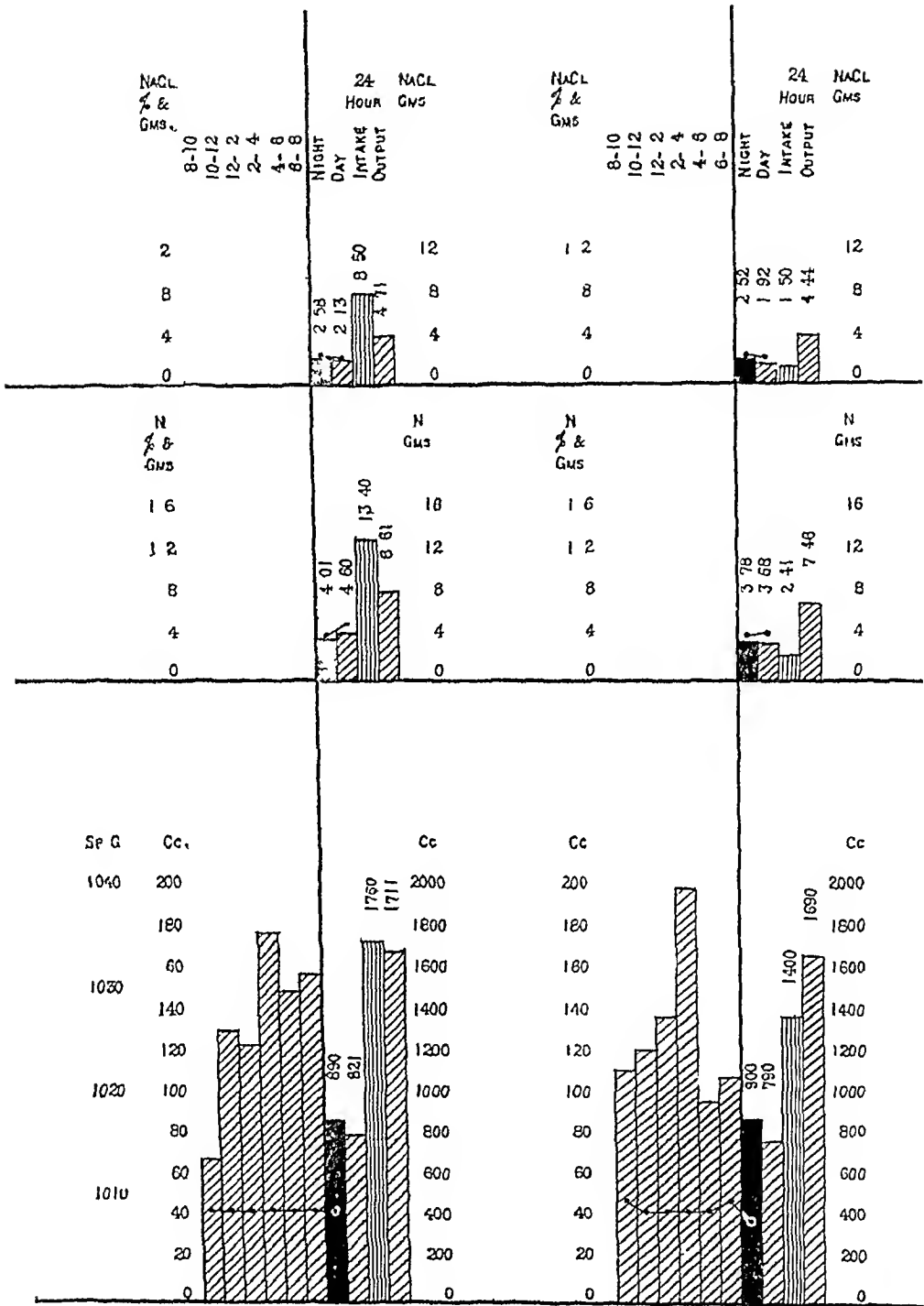
TABLE 14—RESULTS WITH HIGH AND LOW DIETS IN AN ADVANCED CASE OF CHRONIC NEPHRITIS WITH EDEMA. THE MAXIMAL SPECIFIC GRAVITY ON THE LOW DIET IS MODERATELY LOWER THAN NORMAL, THAT ON THE HIGH DIET IS MARKEDLY SO (THE FIGURES CORRESPOND WITH CHART 6)

Time of Day	C C	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	Grams	Per Cent	Grams
8-10	130	1 011				
10-12	118	1 010				
12-2	120	1 011				
2-4	146	1 010				
4-6	150	1 011				
6-8	156	1 011				
Total, day	820		0 37	3 03	0 66	5 41
Night, 8-8	710	1 011	0 46	3 27	0 61	4 33
Total, 24 hrs	1,530			6 30		9 74
Intake	1,760			6 50		12 00
Balance	+230			+0 20		+2 26

Time of Day	C C	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	Grams	Per Cent	Grams
8-10	80	1 016				
10-12	104	1 011				
12-2	96	1 014				
2-4	103	1 014				
4-6	96	1 015				
6-8	86	1 014				
Total, day	565		0 44	2 49	0 66	3 73
Night, 8-8	475	1 014	0 23	1 09	0 63	2 99
Total, 24 hrs	1,040			3 58		6 72
Intake	600			6 00		1 53
Balance	-440			+2 42		-5 19

maximal specific gravity figures for the two tests found in most of the cases with a very low phenolsulphonephthalein excretion (Table 11). The results of the tests in a case of this sort are furnished in Table 15, Chart 7. The results of the two tests are almost identical in every respect. Other tests were made on this patient at various intervals and always yielded similar results.

It may, therefore, be concluded that the maximal specific gravity values obtained with the low and the high diets are of equal signifi-



High Diet Test

Low Diet Test

Chart 7—Results with high and low diets in a case of nephritis of maximal severity, there is absolute agreement between the two tests. In this patient neither the occurrence of a transient myocardial insufficiency nor the temporary presence of a moderate grade of edema changed the results obtained at various times.

cance: that variations may occur but that these are usually caused by the alternate retention or elimination of edematous fluid, and are apparently not influenced by the character of the test diet. Changes in the level of the specific gravity as the result of such a deranged water metabolism, may be extremely rapid or may occur very gradually

TABLE 15—RESULTS WITH HIGH AND LOW DIETS IN A CASE OF NEPHRITIS OF MAXIMAL SEVERITY, THERE IS ABSOLUTE AGREEMENT BETWEEN THE TWO TESTS. IN THIS PATIENT NEITHER THE OCCURRENCE OF A TRANSIENT MYOCARDIAL INSUFFICIENCY NOR THE TEMPORARY PRESENCE OF A MODERATE GRADE OF EDEMA CHANGED THE RESULTS OBTAINED AT VARIOUS TIMES (THE FIGURES CORRESPOND WITH CHAPT. 7.)

Time of Day	C C	Specific Gravity	Sodium Chloride		Nitrogen		Albumin Per Cent
			Per Cent.	Grams	Per Cent.	Grams	
8-10	79	1.009					
10-12	102	1.000					
12-2	110	1.000					
2-4	118	1.000					
4-6	102	1.000					
6-8	100	1.000					
Total ex-	821	.	0.28	2.12	0.56	4.71	10
Ngst, 8-8 ..	890	1.000	0.22	2.55	0.45	4.61	0.8
Total Intake	1,711			4.71		8.61	
Intake ..	1,760			8.50		12.40	
Balance.	-49		-0.79	..	-4.79	

Time of Day	C C	Specific Gravity	Sodium Chloride		Nitrogen		Albumin, Per Cent
			Per Cent.	Grams	Per Cent.	Grams	
8-10	114	1.000					
10-12	114	1.000					
12-2	145	1.009					
2-4	201	1.000					
4-6	93	1.000					
6-8	115	1.010					
Total ex-	790		0.24	1.62	0.45	2.68	10
Ngst, 8-8 ..	990	1.008	0.28	2.52	0.42	3.78	0.8
Total Intake	1,680			4.14	..	7.46	
Intake ..	1,490		...	1.50	.	2.40	
Balance	-200	-2.64	.	-5.06	

THE VARIATION OF SPECIFIC GRAVITY

A study of Table 16 shows that there is no great divergence in the degrees of variation in the specific gravity readings on the high and low diets in abnormal individuals. Of the fifty-six tests exhibiting a subnormal variation on both diets, there are only seven (figures in

heavy type in Table 16) in which the difference between the high and low diets indicated a marked discrepancy. Of those exhibiting a subnormal divergence on only one diet, it appears that an impairment of renal function (figures in heavy type, Table 16) is more frequently manifested on the high (sixteen instances) than on the low diet (nine instances). The reason for this is probably to be found in the relatively greater intake of fluid in proportion to the solid food in the low diet.

The same factors that may cause a fixation of specific gravity in the normal individual (as previously discussed) may also be considered to apply to the abnormal. However, the subject whose renal function is not impaired usually shows a fixation of specific gravity at a high level, while with an impairment of renal function this manifests itself at a much lower point (Table 16). It must be borne in mind that cases of passive congestion of the kidneys and cases of oliguria in either acute or chronic nephritis may all have a tendency to fix their specific gravity at about 1.020. That a low, fixed specific gravity does not admit of one interpretation but must be closely correlated with the clinical findings, may be readily gathered from Table 16. It is obvious that this symptom has an entirely different significance in chronic nephritis with a low phenolsulphonaphthalein output than it has in acute nephritis or cystitis when the phenolsulphonaphthalein excretion is normal or nearly so.

The marked variations that occurred in some of the cases may be largely explained, as were the differences in maximal specific gravity readings on the low and high diets, by sudden or more gradual changes in the response of the kidney to edema. Tables 12, 13 and 14, and Charts 5 and 6 illustrate this very well.

It may be concluded, therefore, that the degree of variation of specific gravity in test meals for renal function is not very different, whether high or low diets be employed.

SUMMARY

Specimens of urine were collected at two-hourly intervals during the day and for a twelve-hour period at night in a considerable number of normal subjects. Various diets were employed while these tests were carried out. It appears that certain characteristics, as indicated by the specific gravity of all the specimens and the volume of the night urine, are present regardless of the diet. These are summarized in Tables 5 and 7, and they may be regarded as the normal standards by which to judge similar tests in abnormal individuals.

A normal individual will void very varying two-hourly specimens, even though the intake of food and fluid is restricted to constant

TABLE 16—COMPARISON OF THE DEGREES OF VARIATION OF SECIFIC GRAVITY ON THE HIGH AND LOW DIETS IN ABNORMAL PERSONS

Diagnosis	Number of Cases with a Variation of 9 Degrees or More on Both Tests	Cases with a Variation of Less than 9 in One Test Only				Cases with a Variation of Less than 9 in Both Tests			
		Degrees Variation Specific Gravity*		Maximal Specific Gravity of Test Showing Least Variation	Phenol sulphone-phthalein Per Cent in Two Hours	Degrees Variation Specific Gravity†		Maximal Specific Gravity of Test Showing Least Variation	Phenol sulphone-phthalein Per Cent in Two Hours
		Low Diet	High Diet			Low Diet	High Diet		
Chronic nephritis	17	8	10	29	53	8	3	12	58
		12	7	15	46	5	7	22	47
		10	3	09	46	5	8	10	40
		10	7	16	45	5	1	11	40
		13	6	15	44	7	4	13	39
		10	4	18	39	6	7	20	38
		7	14	20	35	8	9	19	37
		9	6	18	30	4	3	11	36
						2	3	09	35
						8	2	15	35
						3	2	14	32
						4	3	15	31
						2	7	20	31
						2	3	15	30
						6	7	12	30
						5	7	17	29
						5	5	22	25
						4	2	12	21
						4	5	19	21
						4	2	11	20
						5	1	10	20
						2	3	10	16
						2	4	14	16
						2	3	16	12
						6	1	11	10
						2	1	11	10
						2	0	09	8
						3	3	10	5
						4	0	08	5
						2	1	08	5
						5	1	14	5
						3	4	12	0
						2	1	11	0
Acute nephritis	1	6	13	17	72	1	2	09	61
		13	8	16	54	5	8	14	60
		4	15	14	50	1	2	13	54
						3	5	16	53
						8	6	16	50
						4	3	15	40
						3	5	15	35
Essential hypertension	6					5	2	15	35
						2	3	13	24
		8	12	14	81	7	6	17	79
		9	5	24	78	7	7	10	67
		9	7	18	68	6	6	13	60
		13	6	20	65	6	5	20	55
		13	7	15	59	5	4	24	54
Polycystic kidneys	6	16	8	14	57	5	2	29	54
		8	15	18	55				
		12	5	25	52				
		6	11	19	51				
Cystitis and pyelitis	2					0	1	10	0
						2	1	11	60
						6	5	09	57
Cardiac disease	1	17	7	33	55	7	6	21	40
Anemia	1	17	8	15	55	8	7	19	31
Hyperthyroidism	1	1	14	28		4	3	12	73
Spinal cord lesion and bladder paralysis	3					4	7	17	
No renal lesion	4	13	7	17	75	1	1	12	0
		6	11	24	58				

* The figures in heavy type indicate the test in which the variation is less than 9

† The figures in heavy type indicate the comparative tests in which there was a marked difference (more than 3 degrees) in the variation on the low and high diets

quantities of water taken at two-hourly intervals Under these circumstances there are periods of polyuria with a rather low specific gravity, alternating with oliguria and a higher specific gravity This phenomenon may prove to be a criterion of the amount of fluid necessary to carry on the vital activities of the body If only small amounts are taken, the urine output is low, constant from one two-hour period to the next, and the specific gravity becomes fixed at a fairly high level

Comparative tests on fairly high and low protein diets were carried out in a series of patients afflicted with various diseases that are known to impair renal function It was found that in the main the results agreed regardless of the diet Nocturnal polyuria was more frequent on the high than on the low diet This was evidently due to an effort on the part of the kidney to eliminate solids by means of polyuria when an adequate concentration of solids was no longer possible Nocturnal polyuria, when occurring with a low protein diet, must therefore be regarded as a much graver sign of renal insufficiency than when it occurs with a high protein intake

Marked variations in the results were brought about by the elimination of edema When edema is present, the change from oliguria to polyuria may come about with extreme rapidity and influence the interpretation of renal function, if judged by the urine alone and not by the clinical aspects of the case as well In every instance, as has been previously accentuated, the urinary findings must be correlated with the character of the diseased processes giving rise to the changes in the kidneys, in order that the exact significance of this test for renal function may be appreciated

TACHYCARDIA OF UNKNOWN ORIGIN

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Among the draft registrants examined during the spring of 1918 by the New York Hospital medical advisory boards there were 141 men with organic heart disease and ninety-three with what we will describe briefly as "tachycardias of unknown origin" Further scrutiny of this latter group would probably have shown that a small number were early cases of Graves' disease (exophthalmic goiter) or tuberculosis, and that alcohol was the cause of the rapid heart rate in another small group A surprisingly large proportion of the men suffering from circulatory disease, however, would be found in this group of what we have termed, for want of a better name, "tachycardias of unknown origin"

Fourteen of these men were examined a number of times, their histories being taken carefully and their circulatory reactions to graduated work being determined on at least three occasions Chief importance will be attached to our objective findings, for many of these men either believed that they were not physically fitted for army service or wished to avoid such service, which did not tend to increase the reliability of their histories Our experiments with graduated work led us to classify our fourteen cases into two groups — a severe type and a mild type The reasons for this classification will be given later

FAMILY HISTORIES

Six of our patients gave a history of neurotic taint in the family

S R, aged 21, severe type of case, mother hysterical, father of violent temper, one sister nervous, one brother has pulmonary tuberculosis

S B, aged 23, severe type of case, mother died of melancholia, one sister has melancholia

C G, aged 22, moderate type of case, mother epileptic

F S, aged 28, mild type of case, mother has melancholia, "nervous prostration" and pulmonary tuberculosis

A S, aged 22, mild type of case, mother has "nervous prostration" and hysterical attacks

S F, aged 22, mild case, father's father insane, mother is nervous and has rapid heart action

* Submitted for publication June 19, 1918

HISTORY OF INFECTION

In no one of our five severe cases had the patient ever had acute articular rheumatism, one had had scarlet fever and another diphtheria

The patients in nine mild or moderate cases gave no history of acute articular rheumatism, two had had scarlet fever and one had had three attacks of pneumonia

NATURE AND TIME OF ONSET OF SYMPTOMS

Severe Type of Case—*P P*, for eight years has had pain around the heart, exhaustion and shortness of breath after exercise

S R, when a small boy couldn't play with other boys on account of shortness of breath For five years he has suffered from palpitation and pain around the heart following exercise

S B, for three years has had palpitation and breathlessness after exercising

P R, when a child could not run on account of shortness of breath and cardiac pain These symptoms, evoked by exercise, have persisted

A V, when a small boy had to stop running before his comrades did on account of shortness of breath Has had rapid heart action for the past fourteen years

Mild Type of Case—Two of these nine mild cases gave histories of breathlessness on exertion beginning in childhood One of these histories was probably false The other seven men complained of breathlessness on exertion and palpitation or rapid heart action beginning from one to six years previously

One man (*S F*) occasionally had a stinging pain over the heart after exercise and another (*K X*) complained of substernal pain after exercise

Nine men said that they disliked whisky, one saying that it made his heart beat more rapidly and caused a choking sensation

The physical examination of the circulatory systems was normal in all these cases Occasionally a functional systolic murmur was heard over one of the valvular orifices The lungs were negative and there was no evidence of exophthalmic goiter

METHOD OF EXAMINATION

Each man rested sitting on a chair until the pulse rate became constant Work was furnished by swinging dumb-bells weighing 10, 20 or 25 pounds The same rhythm was maintained in swinging the bells and work was augmented by increasing the number of swings Between the exercises the subjects rested for five or ten minutes

From three to six groups of exercises were given on each day the patient was examined. The men were seen from three to twelve times, several days or a week intervening between the visits.

The pulse was counted in a number of instances immediately after work for fifteen seconds, and in all cases, after 110 seconds had elapsed, for twenty seconds. Thereby the rates immediately after work and at the end of 120 seconds were computed.

The blood pressures were read by the same observer by auscultation, using a Riva-Rocci type of sphygmomanometer. The frequent method¹ of observation was used in every experiment, and the infrequent method¹ in many instances.

REACTIONS TO EXERCISE, CIRCULATORY AND OTHERWISE

Severe Type—There was a small group of men who responded to exercise in a way quite different from normal individuals. In the first place they were able to do much less work than normal men. Their upper limit of work varied between 1,600 and 4,500 foot-pounds performed in the manner previously described, whereas the normal upper limit at 20 to 30 years of age we have found to be between 6,000 and 12,000 foot-pounds. Again, when they reached the comparatively low limits of their efforts they became dyspneic, exhausted and in three instances complained of precordial pain. When a normal person reaches his limit of work his dyspnea may be quite as marked, but his fatigue is rarely as pronounced and persistent as in these cases. The precordial pain is also a symptom rarely found in normal persons.

The facial expression of these persons when they had finished the heaviest work was anxious and indicated unmistakably the distress they felt. The precordial pain was referred to the region below the left nipple and was accompanied by tenderness on pressure of the underlying intercostal muscles.

The production by relatively small amounts of work of the syndrome of symptoms just described is, we believe, of more value in determining the severity of the case than are the pulse rate and blood pressure reactions. This has, accordingly, been our chief guide in classifying our cases.

The reactions of the pulse rate are summarized for both severe and mild cases in Table 1 and those of the systolic blood pressure in Table 2. In Table 1 the expression "overtaxed" signifies that the person suffered from marked dyspnea, fatigue or exhaustion and, in severe cases, from precordial pain.

The pulse rates of the severe type of cases were all higher than normal and all showed greater increases immediately after work than

¹ Barringer, T. B. Jr. *Am Jour Med Sc*, 1918, **155**, 864.

TABLE 1—REACTIONS OF PULSE RATE TO GRADUATED WORK IN CASES OF TACHYCARDIA

Name and Age	Type of Case	Work in Foot Pounds	Pulse Rate			Return to Normal in Sec	Remarks
			Before Work	After Work			
				Immediately	At 120 Sec		
P P 22	Severe	1,600	104	144	116	180	Overtaxed*
		(10 s 20) 2,100	100	144	110	150	
		1,200	116	132	114	120	Overtaxed
		1,800	114	130	124	180	
		(10 s 25) 3,000	112		108	120	Overtaxed
		1,200	92		108	180	Overtaxed
		1,800	92		99	180	
		3,000	92		108	180	
		(10 s 30) 3,600	92		112	180	
		S R 21	Severe	2,000	130	142	108
3,000	122			141	128		
(20 s 20) 4,000	112			156	126	180	
2,000	112				140	180	Overtaxed
2,300	118				120	180	
3,000	112				132	240	
2,100	102				108	Overtaxed	
3,000	104				118		180
(20 s 20) 4,000	100				114	180	
P R 23	Severe			2,000	96		92
		(20 s 15) 3,000	96		112	180	
		2,000	80		100	Overtaxed	
		3,000	80		102		180
S B 23	Severe	2,300	124	148	128	Overtaxed	
		3,400	128	180	132		
		2,300	136	148	136	Overtaxed	
		3,400	136	156	136		
		2,300	88		120	240	Overtaxed
		3,400	92		116	420	
		(20 s 20) 4,000	88		104	300	
		A V	Severe	2,300	92	120	104
3,400	96			136	100		
(20 s 20) 4,600	96			160	112	240	Overtaxed
2,300	92			132	92		
3,400	96			160	116	240	
4,500	100				105	Overtaxed	
6,800	108				114		
7,700	100				117	180	
6,600	100				108	Overtaxed	
7,900	100				108		
(25 s 35) 9,200	102				106		
6,600	90				108	Overtaxed	
7,900	104				117		180
9,200	102				112	180	
K X 27	Moderate	3,700	124		120	Overtaxed	
		5,000	124		136		240
		(25 s 20) 5,500	128		120	Overtaxed	
		4,000	116		124		420
		5,200	128		136	200	Overtaxed
		(25 s 25) 7,000	120		136	240	

* "Overtaxed" signifies that patient suffered from dyspnea, fatigue or exhaustion and, in some cases, precordial pain "10 s 20" signifies a 10 pound bell swung twenty times

TABLE 1—REACTIONS OF PULSE RATE TO GRADUATED WORK IN CASES OF TACHYCARDIA—(Continued)

Name and Age	Type of Case	Work in Foot Pounds	Pulse Rate			Return to Normal in Sec	Remarks
			Before Work	After Work	At 120 Sec		
				Immediately			
C G 22	moderate	3,100	96		100		
		(20 s 20) 4,000	96		102		
		3,100	100		100		
		4,000	92		118	180	
		(20 s 25) 5,000	88		96		Overtaxed
P R 23	Mild	6,000	104	160	114	180	
		7,000	104		120	240	Overtaxed
		8,000	104		140	240	Overtaxed
		2,100	112	148	120	180	
		5,100	116	160	128	300	
		5,300	112	160	124	360	Overtaxed
		6,000	84		105	180	
		9,000	100		120	180	
		10,000	104			300	Sl overtaxed
		6,000	90		120	300	
		7,500	104		124	240	
		9,000	108		160	300	Overtaxed
W R 25	Mild	3,000	112	148	120	180	
		5,400	116		116		
		6,700	112		132	240	Overtaxed
		7,000	112		136	240	Overtaxed
		5,400	100		129	280	
		6,700	100		140	240	
		7,000	100		132	420	Overtaxed
S F 22	Mild	5,100	76		88	240	
		7,700	90		100	180	Overtaxed
		5,100	84		105	300	Sl overtaxed
		6,100	92		102	180	Overtaxed
A S 22	Mild	6,300	88		92		
		9,400	92	152	120	180	
		10,600	100		132	300	Overtaxed
		6,300	104		129	300	
		9,400	100		135	360	
		11,000	112		135	240	Overtaxed
F M 23	Mild	4,700	92	112	96		
		5,200	96	112	108	180	Overtaxed
		9,200	88	136	104	240	Overtaxed
		5,200	88	120	88		Overtaxed
		9,200	92	144	104	180	Overtaxed
L H 22	Mild	2,400	96	136	104		
		3,500	92	140	120	180	Sl overtaxed
		4,800	92	160	124	240	Overtaxed
		2,500	100	120	104		
		4,500	108	144	112		
		5,200	108	156	120		
						180	Overtaxed

TABLE 2—REACTIONS OF SYSTOLIC BLOOD PRESSURE TO GRADUATED WORK IN CASES OF TACHYCARDIA

Name and Age	Type of Case	Work in Foot Pounds	Systolic Blood Pressure				Remarks		
			Before Work	After Work					
				First Reading	Maximum Reading	Delayed Rise			
P P 22	Severe	1,200	122	136	146	No	Dyspnea, fatigue, pain Dyspnea marked, exhaustion, pain		
		1,600	108	128	136	No			
		2,400	116	126	136	No			
		1,600 *(10 s 20) 2,100	122 114	122 122	142 134	No No	Dyspnea marked, exhaustion, pain Dyspnea marked, exhaustion, pain		
		1,200	110	130	134	No			
		1,600 (10 s 25) 3,000	112 114	126 130	136 130	No No			
S R 21	Severe	2 000	130	126	140	No	Dyspnea and fatigue Dyspnea, fatigue, pain		
		3,000	122	118	132	No			
		(20 s 20) 4,000	124	116	130	No			
		1 600	126	114	142	No	Dyspnea, fatigue Dyspnea marked, exhaustion, pain		
		2,000	126	126	140	No			
		2,400	126	124	126	No			
		2,100	110	112	126	No	Dyspnea marked, fatigue pain		
		3 000	112	112	124	No			
		(20 s 20) 4,000	110	106	114	No			
P R 23	Severe	2,000	144	146	156	No	Dyspnea, fatigue, pain, palpitation		
		(20 s 15) 3,000	142	142	152	No			
		2,000	140	144	152	No	Dyspnea marked, fatigue, pain		
		3,000	134	138	152	No			
S B 23	Severe	2 300	122	132	156	No	Dyspnea, fatigue		
		3 400	120	130	148	Yes			
		2,300	130	142	162	No	Dyspnea, fatigue Dyspnea marked, exhaustion		
		3 400	130	138	160	Yes			
		(20 s 20) 4,600	122	128	154	Yes			
A V 28	Severe	2 300	124	144	144	No	Marked dyspnea and fatigue		
		3,400	122	134	134	No			
		(20 s 20) 4,500	116	134	134	No	Marked dyspnea, exhaustion		
		2,300	116	142	142	No			
		3,400	120	136	142	Yes	Marked dyspnea and fatigue		
		2 300	118	144	144	No			
		3,400	114	140	152	Yes	Marked dyspnea and fatigue		
		4 600	112	124	140	No			
		6 900	106	112	142	No	6 wks since 1st observation, daily exercise since Dyspnea and fatigue		
		7 900	102	118	136	No			
		6 600	106	118	140	No	Dyspnea marked, exhaustion		
		7,900	106	124	134	No			
		9 200	102	122	133	No			
		K N 27	Moderate	3 700	152	156	178	No	Dyspnea marked, fatigue pain
				5 000	146	154	168	No	
(25 s 20) 5 500	156			152	156	No			
4 000	148			166	168	No	Dyspnea marked exhaustion pain		
5 200	149			160	168	No			
(25 s 25) 7 000	142			154	160	No			

* "10 s 20" signifies a 10 pound bell swung 20 times

TABLE 2—REACTIONS OF SYSTOLIC BLOOD PRESSURE TO GRADUATED WORK IN CASES OF TACHYCARDIA—(Continued)

Name and Age	Type of Case	Work in Foot Pounds	Systolic Blood Pressure				Remarks
			Before Work	After Work			
				First Reading	Maximum Reading	Delayed Rise	
C G 22	Moder	3,100	120	134	158	No	Marked dyspnea and ex- haustion
		1,000	122	128	160	No	
		(20 & 25) 5,000	122	138	162	No	
A S 22	Mild	6,200	124	150	170	No	Dyspnea and fatigue
		9,400	124	141	158	No	
		10,600	122	130	156	No	
		6,200	122	166	182	No	Dyspnea marked, fatigue
		9,400	124	164	170	No	
		11,000	124	152	162	No	
S P 22	Mild	5,600	126	144	172	No	Dyspnea marked and fa- tigue
		6,700	122	142	162	No	
		5,100	140	158	178	No	Dyspnea marked, exhaus- tion
		7,700	124	154	180	No	
		5,100	134	132	176	No	Dyspnea marked and fa- tigue
		6,100	132	138	174	No	Dyspnea marked and fa- tigue
W R 25	Mild	3,000	148	160	182	No	Dyspnea, fatigue, palpi- tation
		5,400	148	164	182	Yes	
		6,700	146	163	182	Yes	
		7,000	146	174	180	No	
		5,400	146	176	172	No	Dyspnea, fatigue, palpi- tation
		6,700	136	148	178	No	
7,000	124	152	182	No			
P R 23	Mild	7,500	148	158	176	Yes	Dyspnea and fatigue
		8,700	142	144	158	Yes	
		10,000	128	144	150	No	
		6,000	148	154	162	No	Dyspnea marked and fa- tigue
		7,500	146	154	162	No	
		9,000	136	146	152	No	
R D L 26	Mild	5,200	114	120	132	No	Dyspnea, fatigue
		6,600	114	118	124	No	
		7,000	108	120	128	No	Dyspnea, fatigue
		9,000	104	100	122	No	
		9,300	110	100	119	No	
F M 23	Mild	4,700	128	136	142	No	Dyspnea marked, fatigue, vertigo
		6,900	128	142	158	No	
		9,300	128	138	156	Yes	
		4,700	120	142	166	No	Dyspnea marked, fatigue
		6,900	122	144	166		
		9,300	116	132	158	Yes	
L H 22	Mild	5,300	142	152	172	No	Dyspnea and exhaustion
		6,600	140	156	176	No	
		7,900	124	160	181	Yes	

do normal men after the same quantities of work¹ The pulse rate failed to return to normal inside of 120 seconds in sixteen instances when the heart was overtaxed, five times it returned to normal inside of 120 seconds, although the heart was evidently overtaxed, on nine occasions it failed to return to normal inside of 120 seconds, although the heart was *not* overtaxed

The curve of the systolic blood pressure showed several interesting anomalies when compared with the curves of normal individuals "A delayed rise" in pressure ("delayed summit," Cotton, Rapport and Lewis²) following heavy work is an almost invariable finding in normal persons In these persons, both of the severe and mild types, it is seldom found, and when present does not persist as in normal people

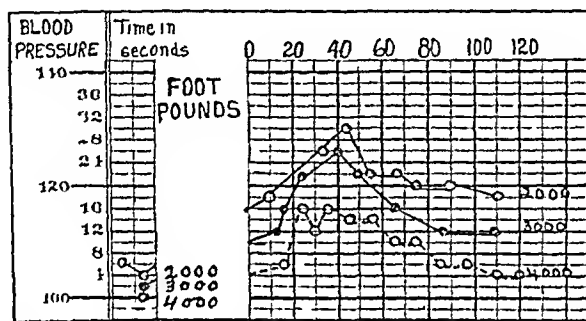


Chart 1—Blood pressure curves ("diminuendo" type) following increasing amounts of work in S R, a severe form of case

The great majority of these patients, both severe and mild, also show blood pressure curves following increasing amounts of work of what may be called a "diminuendo" type The curves, instead of mounting higher and higher as they do in normal persons after increasing quantities of work, fall lower and lower The smallest amount of work was followed by the highest curve and the greatest amount by the lowest curve Charts 1 and 2 exemplify these peculiarities We have observed this type of curve occasionally in cases of cardiac insufficiency after increasing amounts of work

The various reactions to work which we have described make it evident that, whatever the underlying cause of the circulatory condition in this small group of men may be, the heart's reserve power in each one was decreased

One man (A V) was given daily graduated exercises with dumbbells and the excellent effect on the cardiac reserve power may be seen in Table 2

These severe cases resemble closely those described by Lewis and his associates as suffering from "disordered action of the heart"

² Cotton, Rapport and Lewis Heart, 1917, 6, 269

Mild Type—There were nine patients who were placed in this class chiefly because of their ability to perform amounts of work approximately normal without evidencing the symptoms of distress exhibited by the former group. Several of these mild cases (K X and C C) were on the borderland between severe and mild, one of the patients having precordial pain after fairly heavy amounts of work.

The pulse rates were all above normal. Immediately after work they were occasionally higher than those of normal men after similar quantities of work, nineteen times when the heart was evidently overtaxed the pulse rate failed to return to normal inside of 120 seconds; three times the pulse rate *did* return to normal inside of 120 seconds, although the heart was overtaxed, sixteen times the pulse rate failed to return to normal inside of two minutes, although the work had *not* overtaxed the heart.

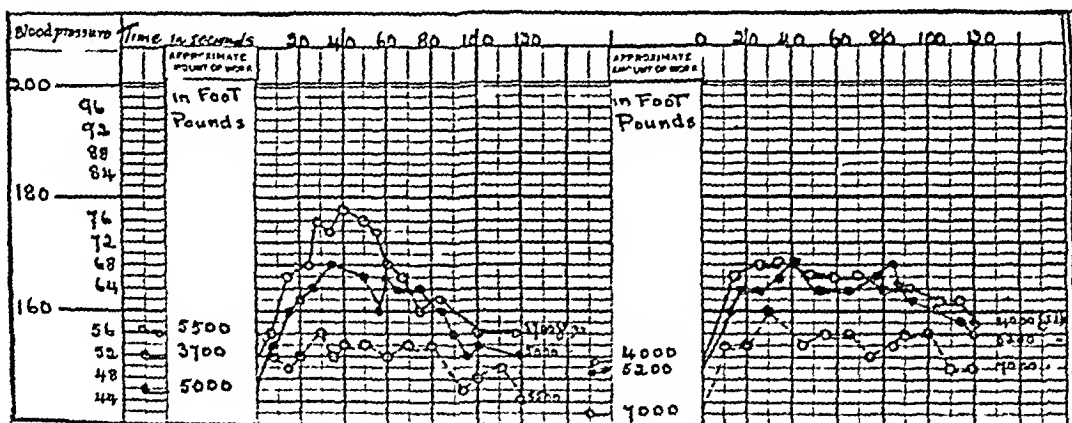


Chart 2—Blood pressure curves ("diminuendo" type) following increasing amounts of work in K. X, a case of moderate severity

The curve of the systolic blood pressure showed more frequently a "delayed rise" after heavy work than did the preceding group of severe types, but it was quite inconstant.

The curves of the pressure following increasing amounts of work frequently showed the "diminuendo" type referred to above.

In these mild types of cases the patients were apparently able to do, without undue distress, about as much work as normal men. The only variations from normal which they showed were the tachycardia, the infrequent presence of a delayed rise in the systolic blood pressure curve, and the frequent presence of a "diminuendo" type of curve.

SUMMARY

The reactions to work of fourteen men with tachycardia, between the ages of 21 and 30, were observed on a number of occasions.

Five men were classified as belonging to a severe type, chiefly because of their inability to perform amounts of work which normal

men are capable of and because the performance of comparatively small amounts of work was accompanied by signs of distress—dyspnea, exhaustion or precordial pain

Reaction of the pulse rates and systolic blood pressure curve to graduated work and their deviations from normal have been described

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THE EFFECT OF THYMUS GLAND INJECTION ON THE GROWTH AND BEHAVIOR OF THE GUINEA-PIG

AN EXPERIMENTAL INVESTIGATION *

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The functions of the endocrine organs have been investigated, for the most part, by three methods, namely, by extirpation of the gland, by feeding normal animals the dried gland or its extracts, and, finally, by the injection into the blood stream or the peritoneal cavity of solutions prepared from the organs. Morphologic studies of these tissues, directed mainly towards discovering evidence of secretory activity, have yielded confirmatory results in some cases, although it must be admitted that the chief effects of these organs are physiologic in nature, affecting metabolism and function in certain ways. Gradually our knowledge of the specific activities of the thyroid gland, the adrenals and the hypophysis, has been becoming exact and definite. The status of our knowledge of the endocrine functions of certain other structures such as the testes, ovary and corpus luteum is not so satisfactory. We are far from possessing any certain conclusive information with regard to the specific hormones of these organs. The thymus gland is likewise a *terra incognita* in spite of the numerous studies which have been made of it during the past few years. In the hope of adding something to our knowledge of this organ, the experiments which form the body of this paper were undertaken.

A review of the literature, a summary of which is given later in this article, shows that the results of previous investigations are far from concordant and mutually confirmatory. Many of the discrepancies are doubtless due to the fact that many different species of animals, standing far apart in the animal scale, have been used for thymus gland experiments. Thus, in the feeding experiments, Abderhalden and Bartlemez used frogs, Gudernatsch used tadpoles, Hoskins albino rats, Klose and Vogt dogs, Paton guinea-pigs. But even where the animals were closely related, the results of much of this work are directly contradictory. Hewer found that thymus gland feeding retarded the development of the testes of young white rats and also

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* From the Psychopathic Laboratory of the University of Chicago, under the direction of Dr. H. C. Stevens

TABLE 1—TABULAR REVIEW OF THE LITERATURE THE RESULTS OF
EXTIRPATION EXPERIMENTS

Author	Publication	Date	Animal Used	Results
1 Abelous and Billard	Arch de physiol	1896	Rabbits, frogs	Great muscular weakness Death in three to fourteen days in frogs In rabbits there were symptoms of intoxication followed by stupor
2			Dogs	Softening of the bones with increased excretion of calcium salts Fractures tended to heal badly, and with less callus, the bones tended to bend
3 Basch, K	Jahrb f Kinderh	1906	Puppies	Muscular weakness and a diminution of intelligence The puppies became sluggish and lost in weight, finally they became very stupid
4 Basch, K	Ibid	1908	Dogs	Bones became soft The excitability of the peripheral nervous system was markedly increased, muscular tremor very pronounced The animals lost in weight, although they continued to eat enormously They finally died
5 Biedl, A	Wien Klin	1903	Hens	Weakness of the legs, tremor of the entire body, and finally death
6 Biedl, A	Ibid	1903	Birds	No observable symptoms
7 Broeze, C	Rev di elm pediat	1905	Rabbits	Reduction of calcium in the bones
8 Colzolari, A	Arch ital di biol	1898	Rabbits	Castration increased the weight of the thymus gland
9 Fischl, Z	Ztschr f Exper Path u Therap	1905	Rabbits, goats, dogs	Negative symptoms
10 Ghika, C	These de Paris	1901	Guinea pigs, rabbits	Castration caused persistent growth of the body, and retarded atrophy of the thymus gland
11 Goodall and Paton	Jour Physiol	1904	Guinea-pigs	There was a diminution of the number of leukocytes, but no apparent change in the rate of growth of the animal
12 Gebele and Miss Hewer	Ztschr f Exper Path	1910	Dogs	Muscular weakness No other changes
14 Henderson, J	Jour Physiol	1904	Rabbits, guinea pigs, bulls, heifers	Castration in guinea pigs, rabbits, and cattle caused a persistent growth and a retarded atrophy of the thymus gland In bulls and unspayed heifers normal atrophy of the thymus was greatly accelerated
15 Hammar, J A	Arch f d ges Physiol	1907	Frogs	No symptoms
16 Hart and Nordman	Berl klin Wchnschr	1910	Dogs	Muscular weakness No other death
17 Kloss and Vogt	Centrabl f Med u Chir	1909	Dogs	Muscular weakness Death eventually occurred from its removal
19 Paton, D Noel	Jour Physiol	1903	Guinea pigs	Castration before sexual maturity was followed by an increase in size of the thymus, and involution of the gland was retarded

TABLE I. SUMMARY REVIEW OF THE LITERATURE. THE RESULTS OF EXTIRPATION EXPERIMENTS (Continued)

Author	Publication	Date	Animal Used	Results
90. Paton, W. Noel	Journ. Physiol.	1905	Guinea pigs	The removal of the thymus gave rise to a more rapid growth of the testes, but no apparent influence on the general growth of the animal
91. Ran I and Thudler	Wien. klin. Wochenschr.	1909	Dogs	Emaciation. The bones became soft and bent easily
92. Sommer and Floerken	Med. Ges. zu Wien	1904	Dogs and cats	Animals were awkward in shape and clumsy; their hair became coarse, their nails rough, and their general behavior stupid
93. Soll, U.	Presse Méd.	1904	Hens, guinea pigs	Laid eggs without shells. Removal of the thymus produced a reduction in the weight of the testicles
94. Trivall and Lo Monaco	Intl. record med. di Roma	1904	Dogs	In only the very young puppies had extirpation any results. There were in these cases disturbances of nutrition, diminished muscular power, diminution of the red blood corpuscles and of the hemoglobin. The disturbance disappeared when the dogs grew older
95. Vincent, S	Journ. Anat. and Physiol.	1904	Frogs	No bodily changes
96. Vincent, S	Proc. Phys. Soc. Journ. Physiol.	1904	Guinea pigs	No symptoms of any kind

caused degeneration in the testes of adult male rats. Hoskins found that feeding albino rats with thymus gland produced no constant effect on the body as a whole or of any particular organs. Paton, employing the same method with guinea-pigs, reported that the growth of the testes was more rapid. Here, in the study of one specific question, namely, the influence of the thymus gland on the testes, one receives three different answers. The method of extirpation has not been more successful than that of feeding. Our reason for this lies in the structure of the thymus gland, in certain forms at least. In the guinea-pig, as Park has recently shown, small masses of thymus tissue are scattered about in the neck adjacent to the main seat of this gland. Obviously, extirpation, under these conditions, can never be complete. The two results which stand out most conspicuously in the extirpation experiments are changes in calcium metabolism and evidence of a reciprocal relation between thymus and testes. With the method of injection, investigators have been concerned for the most part with the immediate results of the injection. They report a fall in blood pressure, acceleration of pulse, dyspnea and diarrhea. In no case, however, have prolonged studies been made by this method. It had seemed to us, therefore, that because of the possibility of incomplete

extirpation and because of the difficulty of causing certain species to feed on thymus gland, the injection method was the method of choice for an experimental attack on this problem. By means of this method one can control absolutely the size and frequency of the dose. Furthermore, we have chosen to determine the effect of this gland on the general metabolism of the guinea-pig as measured by growth of males. A subsidiary problem, namely, the effect of thymus gland injections on the growth of young females, was also studied. The latter results have some bearing on the question of the reciprocal relation between thymus and testes which appears as a result of castration.

TABLE 2—LITERATURE ON THE RESULTS OF FEEDING EXPERIMENTS

Author	Publication	Date	Animal Used	Results
1 Abderhalden, E	Arch d ges Physiol	1915	Frogs	Darker skin, very active, retarded metamorphosis
2 Bartelmez, B W	Anat Record (Proceedings)	1915	Amblystoma, Tigrinum Rana Catesbeiana	In Rana it caused more rapid development. Amblystoma metamorphosed normally, but sooner
3 Gudernatseh, J F	Am Jour Anat	1913	Toads	Stimulated body growth, but inhibited metamorphosis of limbs and tail, hence it has the power to suppress differentiation. They were very active in their movements as contrasted with other feedings
4 Gudernatseh, J F	Arch f Entwicklungsmech	1912	Tadpoles	Thymus feeding gave rise to dark colored skin. A good many died early, presenting a "status thymicus." Growth of body was greatly increased
5 Hoskins, E R	Jour Exper Zool	1916	Albino rat	The results were negative, with no marked constant effect on the body as a whole or on any particular organ. Microscopic examination of the testes showed no degeneration. The apparent decrease in the weight of the male spleen is doubtful
6 Hever, E E	Jour Physiol	1916	White rat	Retarded the development of the testes in the young rats and caused degeneration of the testes in the adults
7 Hewer, E E		1916	White rat	Reduced the development of the testes in the young males
8 Klose and Vogt	Klin u Biol der Thymusdrüse	1910	Dogs	Produced diarrhea
9 Paton, D N	Jour Physiol	1904	Guinea pigs	The growth of the testes was more rapid
10 Romels, B	Arch f Entwicklungsmech	1915	Frogs	Increased body growth considerably, but retarded metamorphosis
11 Salkind, J	Arch d Zool exper et gen	1915	Dogs	Stimulated general growth from a large amount of feeding of thymus gland

General Conditions of the Experiments—Arnheim's preparation of the thymus gland of the sheep was used. The powdered gland was triturated in sterile physiologic salt solution until a uniform suspension was obtained. The initial dose was 1 grain of the dried gland for four weeks. The dosage was increased half a grain every two weeks for six weeks. It was then increased every week for three weeks. During the last two weeks of the experiment the dose was increased twice each week. In no case, however, did the maximal dose exceed 10 grains for each injection. The injection was made with a sterilized needle and syringe into the peritoneal cavity. Each animal used in the experiments was injected twice a week and weighed once a week.

TABLE 3 THE RESULTS OF INJECTION EXPERIMENTS

Author	Publication	Date	Animal Used	Results
1. Abercrombie, E.	Ztschr. f. physiol. Chem.	1912	Dogs	Repeated injections into the peritoneal cavity produced a fall in blood pressure, dyspnea, cramp of abdominal muscle and diarrhea
2. Busch, K.	Ztschr. f. Path. u. Therap.	1912	Dogs	Injections of extracts into the blood stream caused a marked fall of blood pressure
3. Blekel, A.	Med. Wochenschr. Berl.	1901	.. .	Fall of blood pressure
4. Gehele	Beitr. z. klin. Chirurg.	1910	Dogs	Enhancement of the testicles. No increase of body growth
5. Popper, R.	Mitzug, d. k. Akad. zu Wien	1905 1906	Dogs, rabbit	Reduction of arterial tension and dyspnea
6. Patton and Goodhill	Proc. Royal Soc. Edinb.	1905	Guinea pigs	Caused lowered blood pressure with symptoms of suffocation
7. Bychko, K.	Wien. med. Wochenschr.	1909	Dogs	Produced acceleration of the pulse and a marked reduction of arterial tension
8. Vincent, B.	Proc. Physiol. Soc. London	1901	Frogs	No observable symptoms
9. Vincent and Bluen	Ann. Anat. and Physiol.	1901	Guinea pigs	Acceleration of the pulse and a fall of blood pressure
10. Bychko, K.	Arch. f. exper. Path. u. Pharmakol.	1909	Infants	No definite symptoms

To study the effect of thymus gland injection on growth, eight male guinea-pigs of approximately the same age and weight were chosen. Two of these animals were treated with thymus gland; two received a suspension of sheep muscle; two received injections of tenth-normal sodium chlorid solution and two were used as normal controls. To study the influence of sex on thymus gland injections, a series of four female guinea-pigs of the same litter were taken when 15 days old. Two of these animals were given thymus gland injections and two were used as normal controls. The injections of sheep muscle were made in order to have a control on the effect of the injection of sheep protein. By comparing the growth curves of these animals which received the muscle with similar curves for the thymus pigs, the specific effect of the thymus is apparent; the salt solution injections were deemed advisable in order to have a control on the effect on growth of repeated punctures of the abdominal wall and injections of foreign substances into the peritoneal cavity. The growth curves of these animals show that the punctures and injections of sodium chlorid retard growth very little.

From the foregoing data it seems reasonably safe to assume that the thymus gland is in some way responsible for disturbances of growth and development, and, moreover, the evidence thus far produced is also partly in favor of the assumption that the thymus and the lymphatic system are coordinated in function and that the thymus itself is probably concerned with the development of the sexual glands. This does not necessarily mean, however, that the thymus itself is an independent organ, but that it has a general influence in the chemistry of the ductless glands and also in a specific way by itself. Some notable investigators have also shown that a thymus hyperplasia produces a change in the circulation of the thymus which not infrequently is accompanied by sudden death. The thymus gland has also been regarded as a blood-forming organ, and Schaffer¹ is the most recent advocate of this view. He believes, as a result of his studies on cats and rabbits, that the hemopoietic function is like that of the spleen, liver and bone marrow.

TABLE 4—AVERAGES OF GAIN AND LOSS IN WEIGHT OF GUINEA-PIGS IN GRAMS PER WEEK

Thymus				Muscle			
Guinea pig I		Guinea pig II		Guinea pig I		Guinea pig II	
Initial Weight, Gm	+ = Gain - = Loss in Gm	Initial Weight, Gm	+ = Gain - = Loss in Gm	Initial Weight, Gm	+ = Gain - = Loss in Gm	Initial Weight, Gm	+ = Gain - = Loss in Gm
268		284		365		385	
292	+24	285	+1	379	+14	365	-29
301	+33	239	+45	377	+12	421	+36
328	+60	331	+47	402	+37	416	+31
298	+30	391	+107	362	-3	395	+10
	Av +29 2/5		Av +22		Av +12		Av +10
664		624		321		372	
660	-4	638	+14	385	+64	450	+78
653	-11	641	+17	405	+84	489	+117
633	-31	583	-41	417	+96	482	+110
613	-51	587	-37	421	+100	496	+124
617	-47	602	-22	416	+95	468	+96
625	-39	587	-37	433	+112	521	+149
576	-88	541	-33	455	+134	523	+151
608	-56	546	-78	451	+130	538	+166
640	-24	488	-136	452	+131	445	+73
635	-29	536	-88	462	+141	546	+174
	Av -34 6/11		Av -44 7/11		Av +98 9/11		Av +112 6/11

¹ The references will be found arranged alphabetically at the end of the article.

TABLE 5—TABLE OF AVERAGES

Tenth Normal NaOI Solution				Controls			
Guinea pig I		Guinea pig II		Guinea pig I		Guinea-pig II	
Initial Weight, Gm	+ = Gain - = Loss in Gm	Initial Weight, Gm	+ = Gain - = Loss in Gm	Initial Weight, Gm	+ = Gain - = Loss in Gm	Initial Weight, Gm	+ = Gain - = Loss in Gm
452		481		440		402	
478	+26	517	+36	478	+38	426	+24
488	+36	507	+26	496	+56	460	+58
425	-37	550	+69	533	+93	504	+102
552	+100	567	+86	561	+121	419	+17
468	+16	515	+34	482	+42		
475	+23	487	+6	511	+71	453	+51
532	+80	506	+25	575	+135	541	+139
577	+125	516	+35	646	+206	563	+161
552	+100	565	+84	623	+183	551	+149
589	+137	605	+124	660	+220	577	+175
631	+179	626	+145	698	+258	590	+178
650	+198	655	+174	701	+261	638	+236
678	+226	669	+188	741	+301	670	+263
672	+220	724	+243	789	+349	658	+286
688	+236	738	+257	755	+315	655	+253
Av +104 11/16		Av +95 1/8		Av +165 9/16		Av +139 4/5	

TABLE 6—TABLE OF AVERAGES

Thymus				Controls			
Guinea-pig I		Guinea-pig II		Guinea pig I		Guinea-pig II	
Initial Weight, Gm	+ = Gain - = Loss in Gm	Initial Weight, Gm	+ = Gain - = Loss in Gm	Initial Weight, Gm	+ = Gain - = Loss in Gm	Initial Weight, Gm	+ = Gain - = Loss in Gm
100		96		97		89	
116	+16	91	-5	93	-4	92	+3
116	+16	93	-3	110	+13	84	-5
104	+4	104	+8	96	-1	105	+16
124	+24	123	+27	109	+12	123	+34
137	+37	125	+29	138	+41	178	+89
152	+52	142	+46	173	+76	215	+126
169	+69	170	+74	196	+99	239	+150
194	+94	165	+69	230	+133	275	+186
219	+119	187	+91	257	+160	316	+227
237	+137	206	+110	281	+184	340	+251
231	+131	221	+125	327	+230	381	+292
258	+158	249	+153	359	+262	383	+294
Av +65 12/13		Av +55 9/13		Av +92 9/13		Av +127 12/13	

THE EXPERIMENT

Material—April 17, 1917, eight male guinea-pigs of approximately the same size were selected. Each animal was carefully marked and a record of the markings kept. They were paired off as to size and weight and their general behavior noted. Two of the guinea-pigs were used for thymus injection, two for the muscle injections, two for decinormal sodium chlorid injection and two acted as normal controls.

A second series of guinea-pigs, four in number and all females from the same litter, were taken on May 8, when only 15 days old. Two of them were given thymus injections and two were used as controls. This was done to ascertain the difference in effect of thymus injection between the male and female guinea-pigs.

TABLE 7—TABLE OF AVERAGES

Guinea pig I		Guinea pig II	
Initial Weight Gm	+ = Gain — = Loss In Gm	Initial Weight, Gm	+ = Gain — = Loss In Gm
725		727	
672	—113	666	—61
755	—50	723	+4
720	—65	611	—116
676	—100	599	—128
652	—103	646	—81
	Av —73 1/3	604	—123
657		622	—105
637	—20	621	—106
650	—7	622	—105
598	—59	631	—96
628	—29		
661	—4	675	—52
	Av —16 1/3		Av —80 9/12

Interval of Injections—The injections were given twice a week, starting with 1 grain of the powdered gland (Armour). The dose was increased a half grain every fortnight at first, then every week, in the last two weeks of the experiment the dose was increased 1 grain twice each week. An exception was made when the quantity reached 35 grains per injection, this dose was kept up for four injections.

The Weighing—The animals were weighed once a week before the injection was given and before they were fed.

The materials for injection used were

- 1 Desiccated powdered sheep's muscle
- 2 Desiccated powdered sheep's thymus gland
- 3 Decinormal sodium chlorid solution

A summary of loss and gain of body weight in grams per week was as shown in Table 4.

COMMENT AND CONCLUSIONS

Our investigation on the effect of thymus injection on the growth and behavior of the guinea-pig made prominent several features (1) that protein injections give rise to metabolic disturbances, evidenced by the change in rate of growth and in the general bodily signs and symptoms, (2) that more noticeable changes occurred when thymus was injected

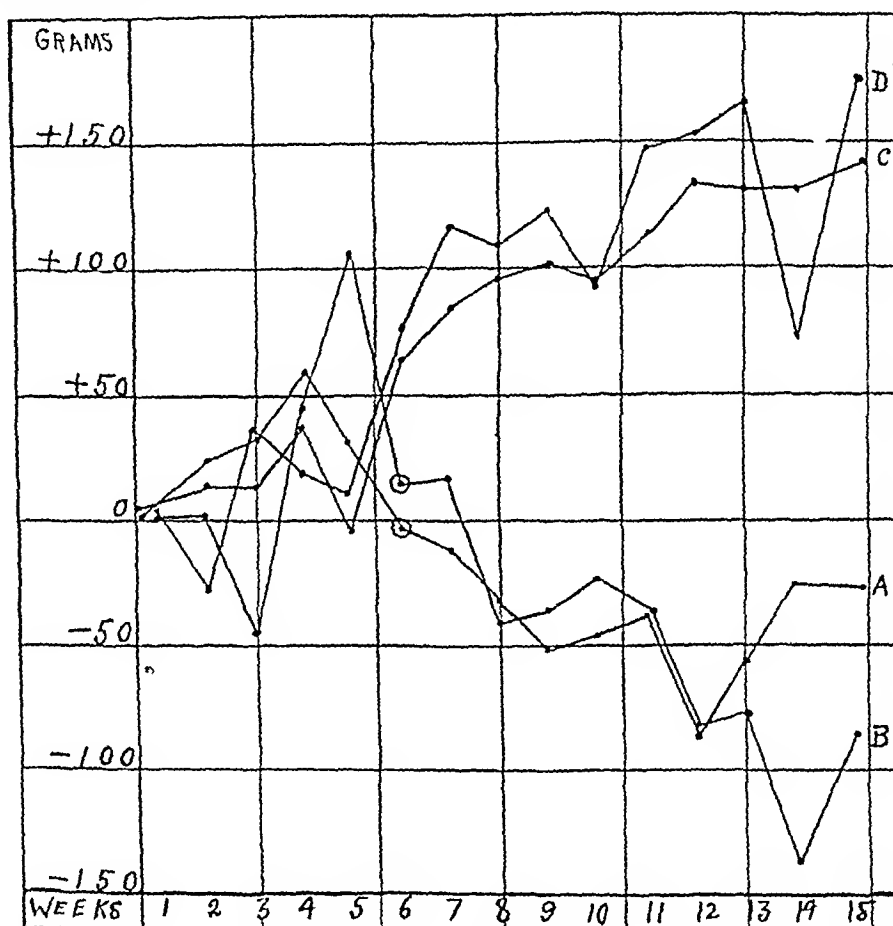


Chart 1—Series I and Series II Comparison of deviations of body weight per week, +=gain, -=loss in grams, A=thymus-injected Guinea-Pig I, B=thymus-injected Guinea-Pig II, C=muscle-injected Guinea-Pig I, D=muscle-injected Guinea-Pig II, all males, O=new guinea-pig

Weintraub and Mayer have shown that thymus feeding causes a striking increase in the output of uric acid. The experiments of Thirloix, Bernard, Abelous, and Billard show that the removal of the thymus in rabbits and frogs gives rise to symptoms of intoxication, proving fatal. When half of the organ is removed, death of the animal does not occur, but the remaining half of the gland becomes hypertrophic. These results suggest that, besides any routine function the thymus may have as lymphatic tissue, it has some more specific effect on the life of certain animals. Basch, König and Tandler, Klose and Vogt found that the removal of the thymus in dogs causes an

increased excretion of lime salts and a deficient ossification of the bones, and in some instances it was followed by coma and death. Svehla's injection of thymus in dogs gave rise to a quickened pulse rate and a fall of blood pressure and dyspnea. Paton and Goodall found that injections of extracts of thymus in guinea-pigs caused a lowering of blood pressure, cardiac weakness, dyspnea, and finally death. Paton's and Henderson's experiments show that there is a reciprocal action between the thymus and testes, each checking the

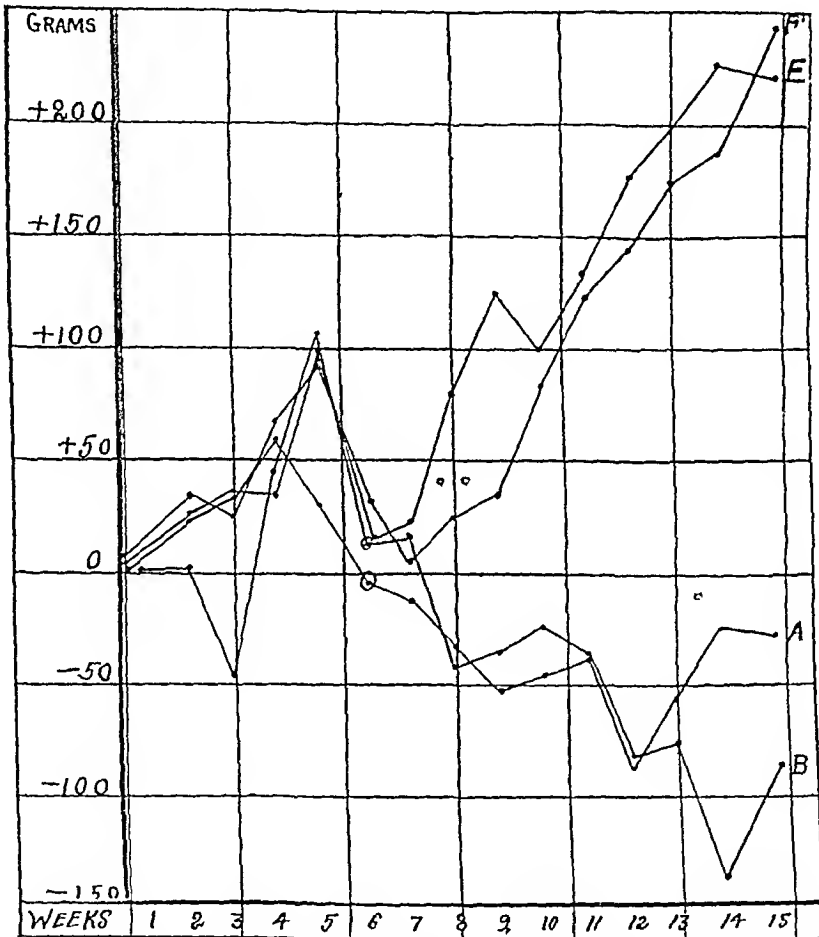


Chart 2—Series I and Series III Comparison of deviations of body weight per week — = gain, — = loss in grams, A = thymus-injected Guinea-Pig I, B = thymus-injected Guinea-Pig II, E = tenth-normal sodium chlorid solution injected Guinea-Pig I, F = tenth-normal sodium chlorid solution injected Guinea-Pig II, all males, O = new guinea-pig

growth of the other. Castration delays involution of the thymus, while removal of the thymus causes a more rapid development of the testes. Various other investigators, such as Ghika, Gudernatsch, Romeis and Bartelmez, found that the thymus possesses vegetative functions, for the feeding of thymus gave rise to larger-sized bodies, but arrested metamorphosis. Soli, Henderson, Gebele, Hewer and

Hoskins have shown that thymus extirpation, thymus irradiation and thymus feeding inhibited the maturity of the sexual glands. As has been said before, another function attributed to the thymus is that of a blood-forming organ.

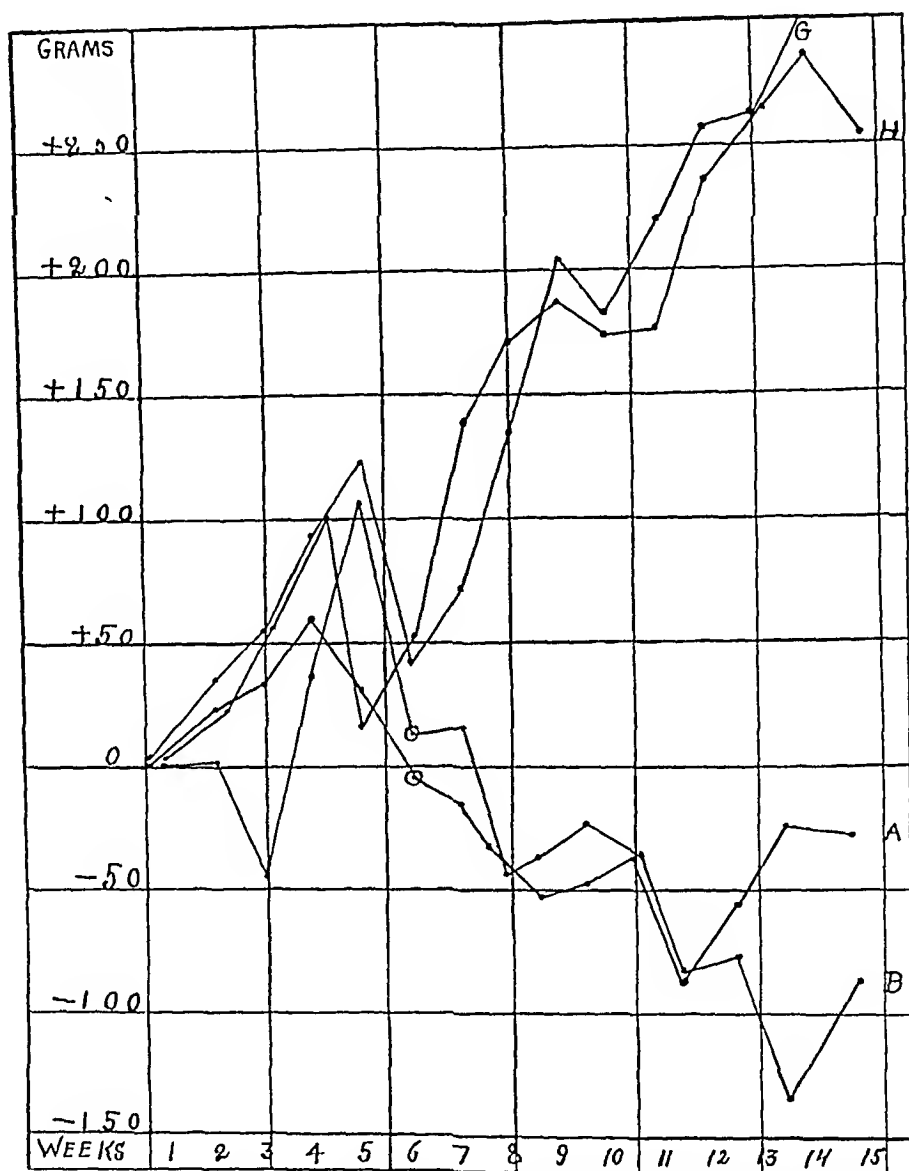


Chart 3—Series I and Series IV Comparison of deviations of body weight per week, + = gain, — = loss in grams, A = thymus-injected Guinea-Pig I, B = thymus-injected Guinea-Pig II, G = control Guinea-Pig I, H = control Guinea-Pig II, all males, O = new guinea-pig

This experiment brought out the fact that when the additional thymus as injected, a change in the body economy took place. This struggle between the animal and the invading protein represents a situation in which disorganization had taken place, and the conflict resulted in a general body loss and in deranged behavior which was made manifest in the symptomatic signs and symptoms.

The significance of this experiment is the evidence it gives of the specific changes caused by the injection of proteins. Among the many and varied signs and symptoms observed after injection were contraction of limbs, contraction of the large trunk muscles, spasms of smaller muscle groups about face and neck, undue bodily movements, overexcitability when the dose injected was comparatively small (1 or 2 grams), sluggishness and extreme cessation of action simulating depression when large doses were given. Another feature was that

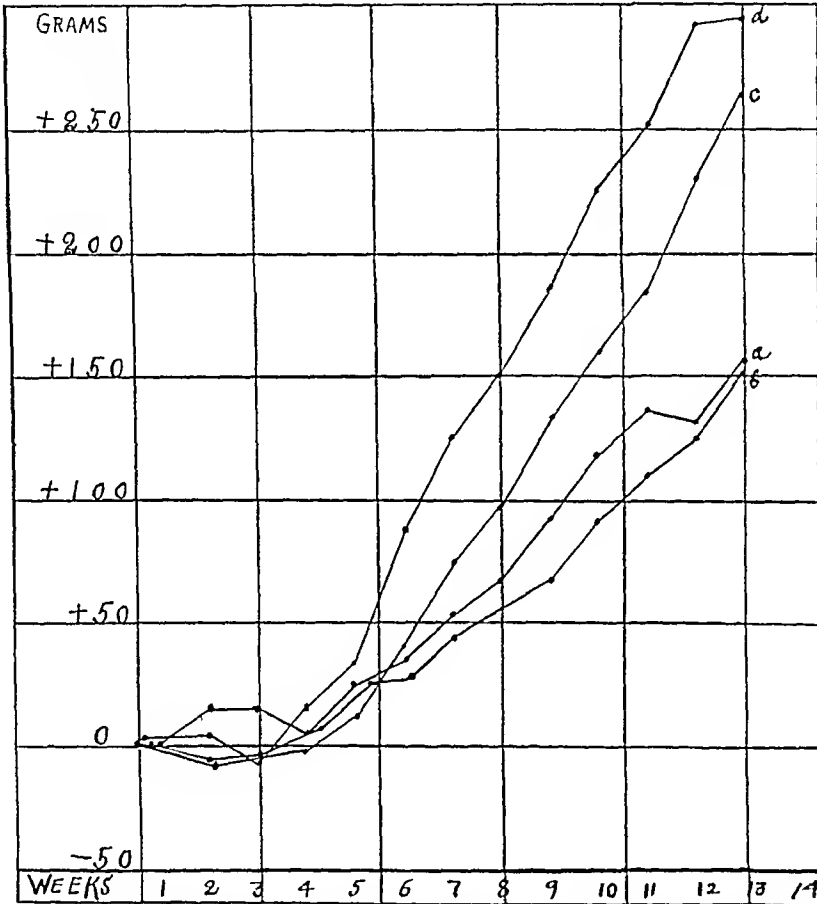


Chart 4—Series V Comparison of deviations in body weight per week, +=gain, -=loss in grams, a = thymus injected Guinea-Pig I, b = thymus-injected Guinea-Pig II, c = control Guinea-Pig I, d = control Guinea-Pig II, all very young females

the hair became dry and rough, and the animals looked emaciated. Dyspnea and convulsions were the outstanding phenomena in the thymus series. In one instance death followed the extreme dyspnea after 4 grams were injected. In two other instances the animals died the afternoon of the day of injection.

These marked effects after thymus injection as compared with the other mediums of the experiment, namely, that of muscle and of

tenth-normal salt solution, call for interpretation of the differences as well of the likeness in the behavior of the guinea-pig. It might be argued that such manifestations in the behavior of the guinea-pig as contraction of limbs, spasms, unrest, excitability, sluggishness, cramps, convulsions, dyspnea and the like, are not measureable entities and therefore ought to be left out in the assignment of a causal connection between thymus injection and behavior. Yet one is scarcely justified in nullifying all such phenomena. When we consider the signs and symptoms that follow the injection of thymus, and compare these animals with those receiving injections of muscle, of sodium chlorid solution, and again with the control animals, it becomes apparent how much more acute and representative are the signs and symptoms that follow thymus injection.

In the case in which a necropsy was had soon after the guinea-pig succumbed to the injection, the blood in the heart and large vessels was found clotted. This finding coincides with the findings of Popper, who says that thymus injected intravenously gave rise to clotting of blood in the vessels. Of course, the clotting might have been produced in the blood stream either from indirect pressure or from substances thrown into the circulation which affect the circulatory or respiratory centers, but this does not eliminate the probability of toxins in the blood stream, as well as a specific entity that plays the rôle of disorganizer, namely, thymus specificity.

The results of our experiment put it within the limits of probability that the thymus gland, whatever its proteolytic rôle common to all animal proteins may be, has a more specific property, namely, that of influencing the bodily growth and behavior of the guinea-pig.

Additional work is necessary also to establish the causal connection between the thymus and its specificity as the gland of internal secretion that regulates growth of the sexual glands and the disorganization of bony structure.

SUMMARY

Since our investigation is of small magnitude, we are justified in drawing conclusions only in so far as our evidence will permit. The most striking and outstanding features are as follows:

1. Reduction of weight in the male guinea-pig was produced experimentally by the injection of thymus gland intraperitoneally.

2. After the injection, well-marked changes took place, namely, muscle spasm, dyspnea, and convulsion.

3. The muscular spasms that occurred after thymus was injected appeared more severe and of longer duration than of either the muscle or of the tenth-normal sodium chlorid injected guinea-pigs.

4 Some animals died after large doses of thymus injection

5 The general appearance of the animals in the thymus series was that of grave metabolic disturbances, emaciation, accompanied by dryness and roughness of their fur

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